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CRANIAL DERMOID AND EPIDERMOID TUMORS

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INTRACRANIAL DERMOIDS and epidermoids, although benign tumors, often remain undiagnosed until their size and extensive spread make complete removal impossible. The purpose of this article is to review the pathology of dermoid and epidermoid tumors of the skull and brain, to report illustrative cases, and to present a follow-up study of 27 patients operated upon at the Toronto General Hospital between 1929 and 1956. In the light of this information, emphasis is laid upon the importance of early diagnosis.

Dermoids are developmental tumors lined by stratified squamous epithelium and containing elements of dermal origin, such as hair and sebaceous glands. Epidermoids, also called cholesteatomas or pearly tumors, are likewise lined by squamous epithelium but contain only keratin, cellular debris, and cholesterol, and lack the hair and other dermal elements which are seen in the dermoid tumor.

DEVELOPMENT

These tumors may arise wherever two ectodermal surfaces fuse together in the developing embryo provided an ectodermal implant is retained deep to the surface. At about the fourth week of intrauterine life, the neural ectoderm separates from the cutaneous ectoderm along the mid-dorsal aspect of the embryo (Fig. 1). If the primitive medullary plate fails to invaginate properly, an epithelium-lined tube or fragment of a tube may persist between the skin and the central canal of the spinal cord or ventricles of the brain. This tube may expand into a cyst at its outer or inner end, or both, and a dermoid or epidermoid tumor may develop. A congenital dermal sinus of varying length and completeness may thus persist in association with these tumors.

This midline inclusion hypothesis does not account for the large number of such tumors that develop in lateral locations. Secondary vesicles, particularly the optic and otic vesicles, develop about the fifth week of intrauterine life, and it is probable that misplaced cell rests associated with these vesicles give rise to laterally located epidermoid tumors. The lateral orbital region is a particularly common site for pearly tumors, and epithelial inclusion at the time of the development of the optic vesicle constitutes the most likely explanation of their origin.

It is possible that trauma may be respon-

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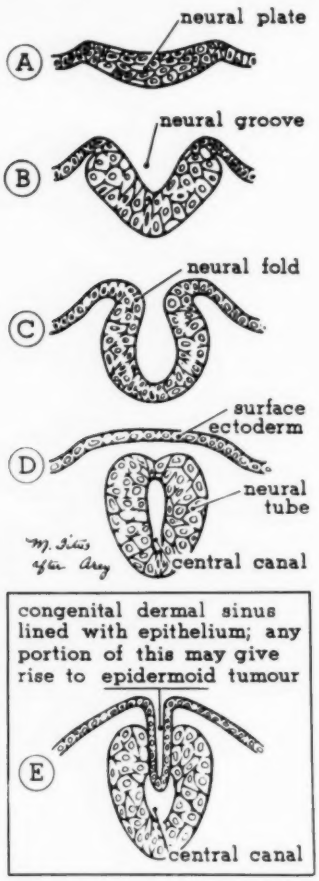

FIG. 1. Showing the normal development of the neural tube along the mid-dorsal aspect of the embryo (*A* to *D*) and formation of a congenital dermal sinus (*E*) that may lead to the production of an epidermoid tumor.

sible for the development of at least some of these tumors. Two of our patients with epidermoid tumors in the anterior temporal region and lateral wall of the orbit had a history of a severe sharp blow to this region many years previously. Perhaps fragments of ectoderm were driven in deep to the skin, and the resulting dermal inclusion gave rise to the tumor.

Finally, one cannot overlook the possibility that dermoids and epidermoids may be the result of differentiation and growth from primitive multipotent embryonic cell rests, in the same way that teratomas are believed to occur.

PATHOLOGY

The epidermoid tumor or pearly tumor is very avascular, and its interior is filled with a dry white crumbly mass, not unlike cottage cheese in appearance. Microscopically, its capsule consists of an outer layer of dense fibrous tissue, inside which is stratified squamous epithelium, some cells showing keratohyaline granules and epithelial bridging. The central material consists of epithelial debris and cholesterol crystals; it is usually solid (Fig. 12) but may be fluid (Fig. 2). The dermoid tumor is filled with amorphous looking tissue, hair, sebaceous and sweat glands, as well as epithelial debris (Fig. 6).

Cruveilhier in 1835 gave a clear account of the appearance of the epidermoid tumor in describing the brain of an 18 year old girl who had been admitted to the hospital in a coma and died shortly afterward. There was an extensive tumor at the base of the brain (Fig. 3). In his words, it was "a bulky tumor, with a most brilliant pearly appearance, surrounded and studded by a group of little elevations resembling a cluster of small pearls of unequal size. It is the product of secretion laid down within a lattice-work of cellular tissue; a fatty tissue, with the consistency of the marrow of bone or of suet. It is encased in a very adherent capsule consisting of layers of crystalline material which gives it the brilliance of silver or pearl."

There are three conditions which may be confused with dermoid or epidermoid tumors, but their fundamental nature is probably different. These are: (1) the cholesteatoma associated with middle ear disease, (2) craniopharyngioma, and (3) the teratoma.

There has been much discussion as to the nature of the cholesteatomas that occur in the middle ear, although they resemble, both grossly and microscopically, the cranial epidermoids that we have been considering.

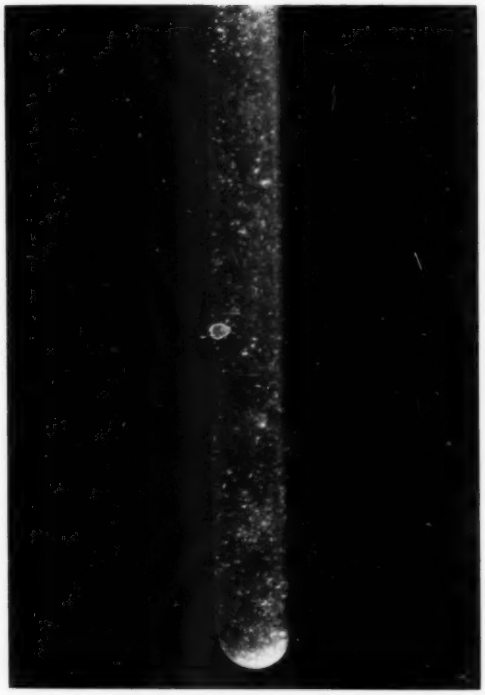

FIG. 2. Fluid from a cholesteatomatous cyst in the parietal lobe of a 17 year old girl.

FIG. 3. Epidermoid tumor at base of brain. From Cruveilhier's *Anatomie pathologique* (3).

In a recent review of this problem Tumarkin suggested three possible theories of origin of the middle ear cholesteatoma: (a) development from congenital inclusion of squamous epithelium; (b) immigration of squamous epithelium from the external ear into the middle ear through a perforated drum; (c) metaplasia of the normal epithelial lining of the middle ear as the result of stimulation by chronic inflammation.

The craniopharyngioma, or Rathke's pouch cyst, has an origin somewhat similar to that of the midline dermoid. It arises from an intracranial remnant of the hypophysial duct which is an extension of epithelium from the pharynx. As seen at operation, it may resemble a suprasellar dermoid tumor.

The teratoma arises by differentiation of embryonic cell rests, and is probably fundamentally different from the dermoid tumor. It is usually found in midline locations. It contains, in addition to ectodermal structures, mesodermal structures such as bone, connective tissue, and muscle. However, it may be wrong to assume a clear distinction between the dermoid and the teratoma, and perhaps the dermoid is a form of teratoma.

CLINICAL FEATURES

Intracranial dermoids and epidermoids produce symptoms by slowly compressing and destroying adjacent structures as they gradually enlarge. The clinical picture may be one of local disturbance of function with focal neurologic signs, or general increase in intracranial pressure with headaches and papilledema. Headaches occurred in over half of our patients. Papilledema was noted in only 2 cases, a fact which emphasizes the extreme slowness with which these tumors

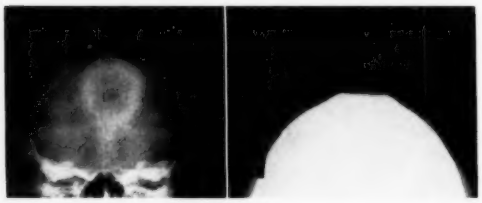

FIG. 4.

FIG. 4. Roentgenograms in Case 1, showing the presence of a midline frontal dermoid tumor.

FIGS. 5 and 6. Photographs of the tumor in Case 1. This was a midline frontal dermoid tumor. Note the presence of hairs.

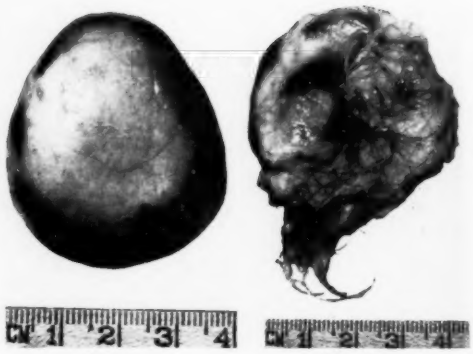

FIG. 5. FIG. 6.

expand, thus allowing time for compensatory cerebral compression and atrophy without great increase in intracranial pressure. Focal neurologic signs were much more common. These varied, according to the location of the tumor, from visual field changes, epilepsy, and hemiplegia to cranial nerve lesions and cerebellar signs. Proptosis was an invariable occurrence in those anterior temporal and frontal epidermoids that invaded the orbit. A skin dimple or sinus in the midline of the occiput or spine may be associated with the presence of these tumors although it was not seen in any of our cases. Spontaneous rupture of the tumor into the ventricle or subarachnoid space may result in aseptic meningitis; this did not occur in any of our cases, but has been reported in several cases by Broager. Aseptic meningitis has been reported as an operative complication by Tytus and Pennybacker.

The age at onset of symptoms was between 15 and 40 years in the majority of our patients. However, the tumor may be silent until much later than this, or may even be an incidental finding at autopsy. One patient with trigeminal neuralgia was 82 years old when the epidermoid tumor of the cerebellopontile angle was first noted. It was successfully removed and the patient was relieved of his pain.

The dermoid tumors tend to appear in younger patients than do the epidermoid tumors. Thus, 5 of 8 dermoid tumors were diagnosed in patients under the age of 20 years, while 14 of 19 epidermoid tumors were seen in patients between the ages of 20 and 40 years. This tendency was also noted in a recent review by Carey.

In most of our patients, the duration of symptoms prior to diagnosis was several years. Only 6 of the 18 patients with a tumor located intracranially had a history of less than 1 year, while 12 had had symptoms for a longer period. Indeed, 4 patients had had symptoms for over 10 years, 4 patients between 5 and 10 years, and 4 patients between 1 and 5 years.

If the tumor involves the skull, as it frequently does, a quite characteristic roentgenographic appearance is seen. There is a central area of radiolucence, surrounded by a clearly defined margin of condensed sclerotic bone, often with a scalloped outline (Figs. 7, 8, and 11). Small midline occipital bone defects may be seen and are evidence of the congenital dermal sinus that may occur in association with these tumors; we have 1 such case. Calcification within a dermoid tumor, sufficient to be visible roentgenographically, is a rare occurrence; it was not seen in any of the cases in our series.

ILLUSTRATIVE CASE REPORTS

The following case reports are chosen as representative of the various types of cranial

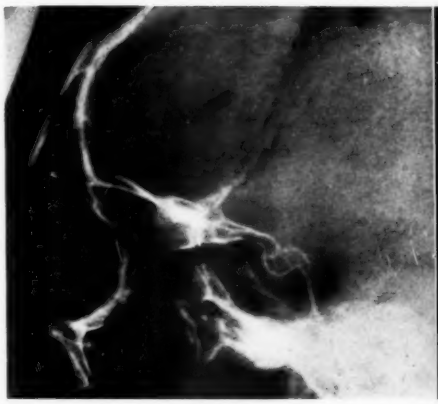

FIG. 7.

FIG. 8.

FIG. 9.

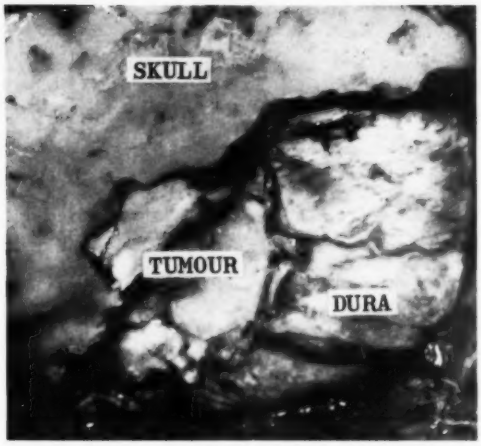

FIG. 10.

FIGS. 7 and 8. Roentgenograms in Case 2, showing the characteristic radiolucent area with sclerotic margin above and lateral to the left orbit produced by an epidermoid tumor.

FIG. 9. Photograph of patient in Case 2, showing the downward and forward displacement of the left globe.

FIG. 10. The tumor in Case 2 as seen at operation. The tumor is the white pearly material lying outside the dura. The overlying temporal bone is thinned and eroded. At the edge of the tumor one may see the tumor capsule.

dermoid and epidermoid tumors, and should serve to illustrate some of the important features of these tumors.

CASE 1. I. S. (Figs. 4, 5, and 6), a 20 year old boy, since birth, had had a swelling in the midfrontal region just behind the hairline. It had been enlarging recently. The mass was the size of a golf ball, and was soft and fluctuant. Roentgenograms showed erosion of the outer table of the skull. At operation there was a cystic tumor firmly embedded in bone and filled with oily amorphous material containing cholesterol crystals and abundant fine hair. The cyst wall was lined with squamous keratinizing epithelium lying on collaginous fibrous tissue. There has been no sign of recurrence to date (4 years postoperatively).

CASE 2. C. McD. (Figs. 7 to 10), a 35 year old man, was seen with proptosis of the left eye. At the age of 7 years he was told he needed glasses because of a weak left eye. For 5 years the vision in his left eye had been badly impaired. For 6 months he had noted drooping of the left upper eyelid, and for 3 months he had experienced stabbing pains in the left temporal region. Examination showed downward and forward displacement of the left globe. There was no ocular muscle paralysis, the pupillary reactions were normal, and the optic disc was normal. Visual acuity in the left eye was limited to counting fingers only. Roentgenograms revealed a circumscribed osteolytic lesion in the region of the lateral part of the roof of the left orbit. The tumor was exposed through a left frontal bone flap. It was confined to the extradural

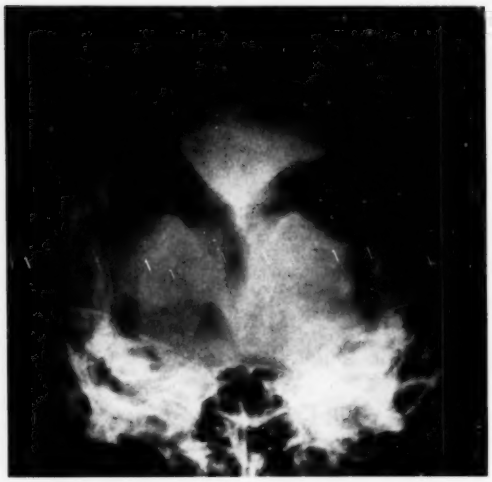

FIG. 11.

FIG. 11. The ventriculogram in Case 3. The large area of scalloped erosion of the occipital bone is characteristic of an epidermoid tumor. This ventriculogram demonstrates the displacement of the fourth ventricle to the opposite side.

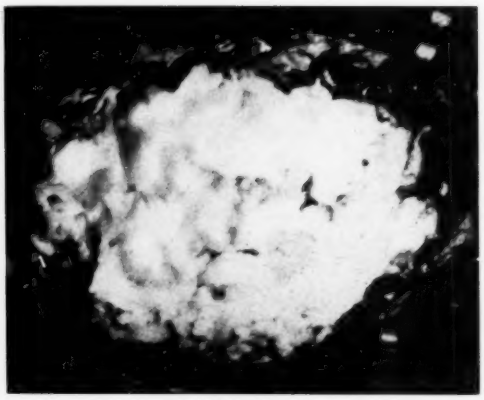

FIG. 12.

FIG. 12. Photograph of the tumor in Case 3, seen at operation. The lesion is an epidermoid tumor in the right occipital region.

space and consisted of white flaky amorphous material surrounded by a fibrous capsule. The overlying bone was thinned and eroded through several places. As the tumor capsule was adherent to the underlying dura, an area of dura was resected. The patient has remained well to date (2½ years).

CASE 3. G. A. (Figs. 11 and 12), a 32 year old man, gave a history of right occipital headaches for 4 months and unsteadiness in walking for 3 months, with a tendency to veer to the right. He had had blurred vision for 2 weeks. There was gross papilledema with retinal hemorrhages bilaterally, and nystagmus was present on looking to either side. There was inco-ordination of the right arm and leg. There was slight tenderness in the right occipital area. Roentgenograms of the skull showed a large irregular area of radiolucence with scalloped margins in the right occipital area. Ventriculogram showed a marked shift of the fourth ventricle to the left, indicating the presence of a mass in the right posterior fossa. At operation there was a large pearly tumor in the right occipital and suboccipital area, completely eroding the bone but confined to the extradural space. The capsule stripped readily from the dura. Microscopically, the cyst wall was identified as an epidermoid tumor. This patient's symptoms and signs rapidly disappeared, and he has remained well up to the present time (5 years).

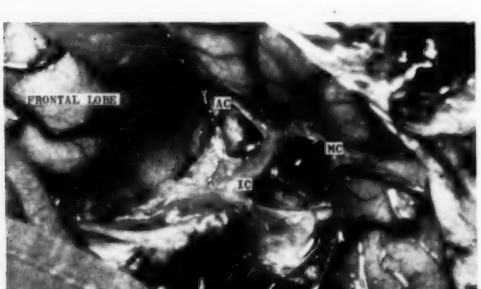

FIG. 13. The tumor bed in Case 4 photographed after the removal of a large pearly tumor. The left frontal lobe is being retracted upward, and the temporal lobe is seen in the lower right-hand portion of the photograph. The internal carotid (*IC*), anterior cerebral (*AC*), and middle cerebral (*MC*) arteries are crossing the field. The remnants of the tumor capsule are visualized as a folded membrane lying upon the floor of the tumor bed.

CASE 4. K. P. (Fig. 13), a 27 year old male, had had a very extensive suprasellar pearly tumor partially removed, and a second operation was necessary 3 years later because of recurrence. In 1946, psychomotor seizures developed, characterized by attacks of auditory disorientation in which he was unable to localize sounds; there would be a queer feeling in the abdomen, and he would forget names during the attack. In 1950, he began bumping into objects on his right side. In 1952, he was found to have a right homonymous hemianopsia, a pale left optic disc, and left sided anosmia. An arteriogram of the left carotid showed straightening of the carotid siphon and elevation of the middle cerebral artery. Ventriculogram showed encroachment on the frontal and temporal horns of the left lateral ventricle and displacement o

FIG. 14.

FIG. 15.

FIG. 14. Photograph of the intraventricular epidermoid tumor in Case 5, seen at operation. The view is taken through the occipital horn of the dilated left lateral ventricle.

FIG. 15. The epidermoid tumor in Case 6 may be seen between the medulla and the right cerebellar hemisphere.

the third ventricle to the opposite side. Operation disclosed a large pearly tumor which started at the left sylvian fissure, extended across the midline, and surrounded the left carotid artery and its branches as well as both optic nerves. A large portion of the tumor and its capsule was removed, but complete removal was not possible. Postoperatively, his visual fields improved remarkably, and except for transient diabetes insipidus, he was well. In 1955, he again noted progressive impairment of the nasal field of the left eye, and operation disclosed a huge recurrence in the suprasellar region. It was not possible to remove all of this as it extended well back toward the clivus and into numerous inaccessible crevices. He has remained well to the time of this report, 1½ years after his second operation.

CASE 5. M. K. (Fig. 14), a 29 year old man, had suffered minor epileptic seizures since the age of 6 years. For 5 years he had had grand mal attacks, often heralded by a musical aura "like some music I have heard before." In 1955, he was found to have a tremor in the right hand and difficulty in performing fine movements with the right hand. There was a right homonymous hemianopsia. Roentgenograms showed a small round clear cut bony defect in the left parieto-occipital region. Air studies showed a well circumscribed multilobulated mass within the temporal and occipital horns of the left lateral ventricle. The occipital horn was greatly dilated and extended to the bony defect in the skull. At operation these findings were confirmed. The dilated occipital horn of the ventricle lay directly under the skull defect, and a large intraventricular pearly tumor was found containing 2½ ounces of porridge-like material. No attempt was made to remove the tumor capsule. Since operation he has been at full time work as a foreman in a paper mill. It is now 2 years since his operation.

CASE 6. B. A. (Fig. 15), a 40 year old woman, had a 10 year history of difficulty with balance and a tendency to fall to the right. There had been right-sided tinnitus for 8 years. Three years ago, there had been transient numbness of the right side of the face. For 1½ years there was increasing weakness and clumsiness of the right arm and leg. Examination revealed impairment of the right fifth, seventh, eighth (vestibular and auditory), ninth, and tenth nerves. There was nystagmus on looking to the right, and inco-ordination of the right arm and leg. The roentgenograms of the skull were negative and the cerebrospinal fluid protein was not raised. Ventriculogram showed a marked shift of the fourth ventricle to the left. At operation she had a pearly tumor in front of and to the right of the medulla and pons, stretching the ninth, tenth, and eleventh nerves and surrounding the fifth and seventh nerves. A tongue of tumor extended up through the hiatus tentorii. The tumor was incompletely removed and the dura left open. There was some transient increase in her neurologic deficit postoperatively, but this condition has improved and

TABLE I.—LOCATIONS OF TUMORS

	Dermoid	*Epidermoid*	*Total*
Intracranial (intradural or extradural, sometimes difficult to differentiate)			
Base of brain:			
Suprasellar	2	3	5
Parasellar		2	2
Lateral ventricle		1	1
Third ventricle	1		1
Intracerebral (parietal or temporal)		2	2
Posterior fossa:			
Cerebellopontile angle		3	3
Prepontile		1	1
Fourth ventricle		2	2
Lateral suboccipital		1	1
	3	15	18
Cranial or extracranial (with no displacement of dura)			
Midline frontal	4		4
Parietal		1	1
Lateral orbital			
With displacement of globe and dura	1	2	3
No displacement of globe or dura	1		1
	6	3	9
Totals	9	18	27

the patient has remained well to the present time (1 year).

FOLLOW-UP STUDY

Between the years 1929 and 1956, 27 patients with dermoid and epidermoid tumors of the skull and brain have been operated upon at the Toronto General Hospital. This represents an incidence of slightly less than 1 per cent of all the verified brain tumors seen during this period. All except 2 of these patients were adults, as patients under 14 years old are not as a rule admitted to this hospital. None was seen with meningitis, and none had a congenital dermal sinus or midline dimple, features which are more commonly encountered in children. Table I shows the locations of the various tumors. In some cases, only a small biopsy was available for microscopic study so that a dermoid might have been wrongly diagnosed as an epidermoid. Some of the locations which are given in this tabulation may be misleading, because a tumor might be classed as lateral when it really had its origin in the midline and later extended laterally.

From Table I it is evident that epidermoid occurred twice as frequently as dermoid tumors. It is also clear that the epidermoid tumors have a tendency to occur in lateral locations, while dermoid tumors are more commonly situated in the midline.

SURGICAL MANAGEMENT

The majority of patients with cranial or extracranial tumors are permanently cured by complete removal, and there has been no recurrence among our 9 patients. The difficulty of complete removal of some of the intracranial tumors may be realized when one sees how widespread these tumors may be, extending and burrowing under the base of the brain, across the midline, and into numerous rather inaccessible crevices, enveloping and surrounding arteries and nerves.

It may be impossible to remove the entire tumor and its capsule. Evacuation of the cheesy content is usually fairly complete, with resultant alleviation of symptoms. Growth from the remaining portion of the capsule may be so slow that many years may elapse before signs of recurrence are evident. So far in our series, signs of recurrence have been known to develop in only 1 patient (Case 4).

There have been 2 operative deaths in the series, one of a patient with an epidermoid in the fourth ventricle operated on in 1934, and the other of a patient with a suprasellar dermoid who died of postoperative infection in 1936 Unfortunately, 4 patients have not been traced. Eleven patients are well at the present time. Our longest follow-up study is of a patient who had a large intratemporal cholesteatoma removed 24 years ago and is still alive and quite well. Three patients with suprasellar dermoids or epidermoids are still well, without signs of recurrence, respectively 13, 11, and 10 years after surgery. One patient with an epidermoid tumor of the cerebellopontile angle is still well after a period of some 7 years.

CONCLUSIONS

A series of 27 adult patients with surgically verified dermoid and epidermoid tumors of the skull and brain is reviewed. Although these tumors probably arise from a developmental defect in early intrauterine life, they may not produce symptoms until the third or fourth decade or even later. Dermoid and epidermoid tumors are benign and very slow growing, and often have a history of several years' duration. They are curable by complete removal, and a plea is made for early diagnosis. Even if the tumor has spread extensively and total removal is impossible, incomplete removal may render the patient symptom-free for a great many years.

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PREGNANCY AND CARDIORESPIRATORY FAILURE IN BOECK'S SARCOID

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THE COEXISTENCE of Boeck's sarcoid and pregnancy is being reported with increasing frequency. Although sarcoidosis may involve many different organs, most important to the obstetrician is the involvement of the heart and lungs.

Reports differ in their interpretation of the effects of Boeck's sarcoid and pregnancy on each other. Some reports in the American literature indicate that the lesions of Boeck's sarcoid regress during pregnancy. Reports from Sweden indicate that the pregnant state may be associated with the appearance of sarcoidosis. On the other hand, our own experience (3, 4), as well as the experience of others, suggests that neither the pregnancy nor the disease are influenced by the other.

This article is concerned with the detailed account of a patient with Boeck's sarcoid who underwent a successful pregnancy despite respiratory insufficiency of marked degree. A somewhat similar type of case, but with death of the mother during the thirteenth week of gestation, was mentioned in Krupp's report on maternal mortality at the Charity Hospital in New Orleans. Several factors which are of particular interest to obstetricians are stressed in this report: (1) the influence of pulmonary lesions on respiration during pregnancy, (2) the management of sarcoidosis in pregnancy, and (3) the prognosis for a successful termination of pregnancy in a patient with pulmonary involvement due to Boeck's sarcoid.

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CASE REPORT

L. G., a 28 year old negro, gravida 2, para 0, former department store employee, was first seen at the Antepartum Clinic of the Columbia-Presbyterian Medical Center on October 2, 1957. Her last menses had occurred on June 3, 1957, and her expected date of confinement was March 10, 1958. The patient's first pregnancy in 1951 terminated at 10 weeks by spontaneous abortion.

Past history revealed that the patient was seen for the first time at this hospital in December 1952, with complaints of pain in the left side of the chest, increasing exertional dyspnea, cough, and severe loss of weight of approximately 1 year's duration. A survey photofluorogram of the chest taken 14 months before (Fig. 1) had been interpreted as indicating negative results. Results of tuberculin tests were persistently negative. The patient was born in Florida and moved to New Jersey at 5 months of age. Her mother had Boeck's sarcoid diagnosed by skin biopsy in 1944. The patient's physical findings were limited to the chest and included harsh breath sounds and musical rhonchi over both lung fields as well as accentuation of pulmonic second sound. Lymphadenopathy was not present. X-ray examination of the chest revealed a lesion involving both upper lobes, suggesting tuberculosis or Boeck's sarcoid. The patient was admitted to Seaview Sanitorium where repeated sputum cultures failed to document a diagnosis of tuberculosis. She was discharged after 3 months and remained unchanged for the ensuing 3 years. In April 1956, dyspnea developed and progressed to the point where she could not get out of bed. This was associated with paroxysmal nonproductive cough, orthopnea, and boring pain of the left side of the chest. Result of a Kveim test was reported as negative in July 1956.

She was admitted to the Medical Service of the Presbyterian Hospital on October 11, 1956. Physical examination revealed a well developed colored female in moderate respiratory distress with a respiratory rate varying between 28 and 44 per minute. Examination of the chest showed fine crepitant rales throughout both lung fields, and tubular breath sounds over the left upper lobe. Laboratory studies revealed a hemoglobin of 14.5 grams; hematocrit of 44; erythrocyte sedimentation rate of 17; white blood count 7,200

FIG. 1.

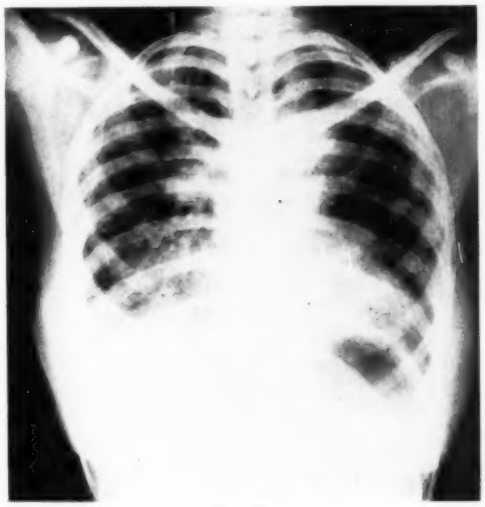

FIG. 2.

FIG. 1. Survey photofluorogram taken in conjunction with application for employment October 3, 1951. Lung fields interpreted as within normal limits.

FIG. 2. Roentgenogram of chest, October 12, 1956, 1 year prior to pregnancy showing widespread pulmonary densities tending to obliterate the margins of the heart and mediastinum. There is some hilar elevation bilaterally. This picture was thought compatible with pulmonary sarcoidosis.

with 54 per cent eosinophiles, and 2 per cent basophiles. Urine analysis was negative. Venous pressure was 90 millimeters of saline and the circulation time was 8 seconds. Results of Mazzini and liver function tests were negative. Blood urea nitrogen was 8; carbon dioxide content 26.5 milliequivalents per liter, serum sodium 142.3 milliequivalents per liter, and serum potassium 4.0 milliequivalents per liter. Total serum protein was 8.4 grams per cent and the partition was 3.9 grams of albumin and 4.5 grams of globulin. An albumin globulin partition 6 months earlier in the clinic was 4.2 grams and 3.4 grams, respectively. Results of coccidioidin, histoplasmin, blastomycin, and tuberculin tests were all negative. A gastrocnemius muscle biopsy failed to reveal evidence of Boeck's sarcoid. Results of an electrocardiogram were within normal range. Repeat roentgenograms of the chest revealed marked increase in the pulmonary infiltrates throughout both lung fields and elevation of both hilar shadows (Fig. 2). Laminograms failed to reveal any pulmonary cavitation.

During this admission, pulmonary function studies were carried out and the results are shown in Figure 5. The patient was hyperventilating with a minute ventilation that was twice predicted. The vital capacity was markedly diminished to 25 per cent of the predicted value. Arterial oxyhemoglobin saturation and carbon dioxide tension were normal, but the diffusing capacity ($D_{L_{CO}}$) was very low. These physiologic findings were all consistent with the diagnosis of "alveolar-capillary block," described by Austrian and associates. She was discharged on October 23, 1956, on a regimen of 30 milligrams of prednisone daily to be followed up in the chest clinic.

She showed slight subjective improvement over the next few months but was unable to perform ordinary household duties without discomfort. Her cough and pain in the left side of the chest subsided, but marked exertional dyspnea and tachypnea persisted. Serial roentgenograms of the chest during this time showed no interval changes. On August 26, 1957, she reported to the chest clinic with a history of amenorrhea of 2 months' duration. On September 10, 1957, she was admitted to the Sloane Hospital for Women for evaluation. The patient exhibited obvious dyspnea on talking. Relevant physical findings were: tachypnea at rest, mild tachycardia, and bilateral diffuse harsh breath sounds with a prolonged expiratory phase. A very loud pulmonic second sound was noted. There was no lymphadenopathy, hepatosplenomegaly, ankle edema, or clubbing of the digits. Pelvic examination disclosed a uterus consistent with a 3 months' gestation. Roentgenograms of the chest showed no change in pulmonary densities.

The patient was considered for a therapeutic abortion. Although she no longer suffered from cough and chest pain she still had marked dyspnea and the roentgenograms were unaltered. Because of her desire to con-

FIG. 3.

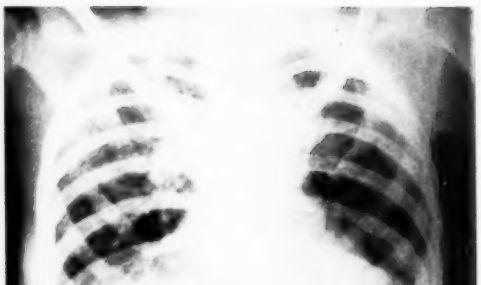

FIG. 4.

FIG. 3. Roentgenogram of chest, January 24, 1958, during thirty-fourth week of gestation. The picture is unchanged except for changes induced by pregnancy including slightly elevated diaphragm and increased pulmonary vascular markings.

FIG. 4. Roentgenogram of chest, February 12, 1958, 1 week following delivery. The diaphragm is lower and the pulmonary vascular markings are decreased. However, there is persistent, unchanged pulmonary parenchymal infiltration.

tinue this pregnancy and because of the clinical appraisal the pregnancy was not interrupted. She was then discharged to antepartum care.

During the succeeding 4 months, the patient's clinical status remained unchanged. On January 23, 1958 she was admitted to the hospital for rest prior to delivery. Physical examination on admission showed a temperature of 98.6 degrees F., pulse 80, respirations 24, blood pressure 118/70. Ascultation of the chest revealed bilateral harsh breath sounds and rhonchi. The left border of cardiac dullness was between the midclavicular line and the anterior axillary line. No murmurs or gallops were present. The fundus measured 6 fingerbreadths above the umbilicus and the fetal heart was heard in the left lower quadrant at a rate of 128 per minute. The cervix was described as closed and long. There was no edema. Laboratory data revealed: hemoglobin 10.6 grams; white blood count 6,550, neutrophiles 64 per cent; lymphocytes 35 per cent; monocytes 1 per cent; venous pressure 115 millimeters of saline, circulation time 13 seconds; erythrocyte sedimentation rate 60; serum calcium 9.5 milligrams per cent. Roentgenograms of the chest showed no appreciable change except for elevated diaphragm and increased pulmonary vascular markings consistent with this stage of gestation (Fig. 3).

Following admission, prednisone was omitted from her regimen. On January 27, 1958, the fourth hospital day, her temperature rose to 102.4 degrees F., with the respiratory rate 48 per minute. She appeared acutely ill. There was sudden onset of nonproductive cough and orthopnea. Her pulse rate was 140. The rhonchi were no longer diffuse, but were confined to the right base where coarse rales were also audible. These findings were consistent with the diagnosis of pneumonia. There was a grade II systolic murmur over the pulmonic area. There was no clubbing of the digits, edema of the ankles, or engorgement of the neck veins. The liver edge was palpable at the costal margin and was slightly tender. The fundus measured 5 fingerbreadths above the umbilicus and was irritable. The vertex was dipping deeply into the lower uterine segment, and the cervix was now 1 finger dilated and 50 per cent effaced. Laboratory studies revealed a white count of 11,000 with 84 per cent neutrophiles; electrolytes within normal limits except for a serum carbon dioxide content of 19.0 milliequivalents per liter. Hemolytic Staphylococcus aureus was grown out of a throat culture, resistant only to penicillin. An electrocardiogram obtained at this time showed a flattening of the T waves in leads V_4 and V_5 suggesting myocardial disease. The possible causes of this patient's sudden difficulties were thought to be either pneumonia or right ventricular heart-failure, and/or recrudescence of the underlying pulmonary disease following withdrawal of prednisone. Because of the urgency of the situation the patient was treated with penicillin, streptomycin, chloromycetin, digitox-

in, and oxygen; prednisone was restarted at a dosage of 30 milligrams orally per day. During the succeeding 4 days, there was gradual improvement. The respiratory rate fell to 32 and the pulse to 100. She was afebrile and the lungs were clear. On February 5, 1958, at the thirty-sixth week of gestation, pelvic examination revealed a ripe cervix and a clinically adequate gynecoid pelvis. Because it was thought that a state of maximum clinical improvement had been reached it was decided that the patient should be induced. She was sent to the labor room for pitocin induction.

Induction was successfully carried out by the use of intravenous pitocin. Following a labor of 2 hours and 55 minutes, under caudal analgesia and anesthesia, the patient delivered a 2,175 gram living male infant after a right mediolateral episiotomy. The second stage was shortened to 4 minutes by the use of low forceps. The placenta was expressed intact. The third stage was marked by uterine atony, responding readily to massage and intravenous pitocin. The estimated blood loss was 400 cubic centimeters. Immediately after delivery there was a dramatic improvement in the patient's clinical state. Her respirations were easier and slower, and each breath was deeper. Her diaphragm moved freely. She was perfectly comfortable outside of an oxygen tent. Her heart rate was 100 and the respirations 24. She was ambulated on the first postpartum day. An electrocardiogram revealed the T-wave changes reverting toward normal.

The puerperium was complicated by a lower urinary tract Bacillus pyocyaneous infection which responded to terramycin. There was a transient elevation of the blood urea nitrogen from 11 to 36 milligrams per cent. Following subsidence of the kidney infection, the blood urea nitrogen returned to normal. Digitoxin was discontinued prior to discharge. Laboratory data post partum included: serum calcium 10.0 milligrams per cent; serum phosphorus 3.9 milligrams per cent; cephalin flocculation and thymol turbidity normal; serum sodium 134.8 milliequivalents per liter; serum potassium 4.61 milliequivalents per liter; carbon dioxide content 26.3 milligrams per cent; serum chloride 105.6 milliequivalents per liter. The patient was discharged on February 15, her tenth postpartum day. A roentgenogram of the chest taken 1 week post partum was essentially unchanged from the one taken on admission. On March 19, 1958, on her 6 weeks postpartum check-up, the patient was free of symptoms except for dyspnea on moderate activity. Her pulse was 92 and respiratory rate 20.

The infant reacted normally following delivery, showing no signs of adrenal cortical insufficiency. On the first day, 2 harsh systolic murmurs were heard. An electrocardiogram showed results within normal limits and a roentgenogram of the chest revealed the heart to be normal in size. The diagnosis of congenital heart disease was made. He received artificial feedings and was discharged in good condition on February 26, 1958, at 3 weeks of age, to be followed up in the Pediatric Clinic.

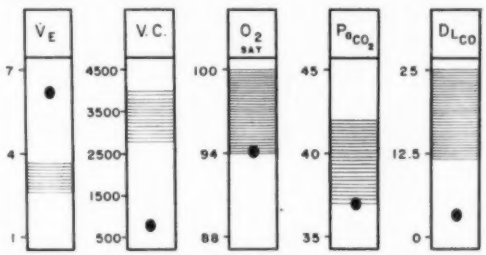

FIG. 5. Pulmonary function studies prior to pregnancy. The chronic hyperpnea, the concentric reduction in lung volumes, the normal arterial oxyhemoglobin saturation, and the low diffusing capacity are all consistent with diffuse involvement of the alveolar-capillary septa by the lesions of Boeck's sarcoid.

DISCUSSION

Boeck's sarcoid is known to cause pulmonary insufficiency by virtue of diffuse involvement of the alveolar-capillary septa. With the advent of steroids for therapy, the prospect arose that these lesions which interfered with alveolar-capillary gas exchange could be made to regress. However, the nonuniform response of patients with virtually identical pulmonary shadows on roentgenograms has led to the suggestion that the anatomic nature of the individual lesions influences the therapeutic response to steroids. Thus, an exudative (soft) lesion is considered to be susceptible to the action of steroids while a fibrotic (hard) lesion is regarded to be refractory to such treatment.

Pregnancy is associated with a heightened production of endogenous steroids. Since our patient had failed to show dramatic improvement while receiving exogenous steroids prior to pregnancy, it could be anticipated that the endogenous steroids of pregnancy would also fail to improve the chest disease. Although this premise was borne out by the course of the patient during pregnancy, the precipitation of pulmonary insufficiency following withdrawal of the prednisone implies that exogenous corticoids may prevent progression of the lesions even though they may be unable to cause their resolution.

This patient was managed in accord with the previous experience at Sloane Hospital which suggests that pregnancy and sarcoidosis do not influence each other's course. Nonetheless, even though the pulmonary disease were to remain static during the course of the pregnancy, the patient still had to face the maximum cardiorespiratory stress of the seventh and eighth months of pregnancy. This has been shown to involve a large blood volume, a rapid heart rate, an unusually high cardiac output, and the retention of salt and water. It is therefore of interest that this patient was able to tolerate the combination of pulmonary insufficiency and the progressive circulatory overload until the thirty-fifth week of gestation. Only with the advent of pneumonia was there a break in medical control.

With the complication of pneumonia, respiratory embarrassment became severe and heart failure became manifest. At that time, even though pelvic examination revealed a favorable cervix and even though uterine irritability was present, induction of the patient was deferred until cardiac and pulmonary failure were again under control. As described by Thomson and associates, following stabilization, the usual practice of the Sloane Hospital for delivering patients with cardiac disease was applied: pitocin induction was carried out using caudal analgesia and anesthesia; the second stage was shortened to 4 minutes by the use of forceps.

Although pregnancy, delivery, and the postpartum course were successfully survived by the patient, the infant was apparently born with a congenital cardiac defect. The infant was artificially fed to spare the mother the circulatory stress of lactation and to avoid a possible untoward effect of lactation on sarcoidosis. No other special precautions were observed for the infant except careful scrutiny over the first 96 hours for signs of adrenal cortical insufficiency.

SUMMARY

1. The case history of a patient with pulmonary sarcoidosis complicated by pregnancy is presented.

2. During the course of pregnancy, cardiorespiratory failure ensued.

3. The medical and obstetric management of this type of patient is analyzed with respect to the role of steroids, the management of labor, and the influence of lactation.

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EXPERIMENTAL STUDIES ON SURGICAL AMELIORATION OF ASCITES IN DOGS

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SURGEONS have attempted the permanent drainage of ascites since the late nineteenth century. Numerous reports have appeared in the literature, mainly of small series of cases and of a wide variety of methods. None has, however, proved uniformly successful, and so attempts to develop some technique by which these patients may be benefited continue. The conservation of the protein and electrolytes sequestrated in the peritoneal cavity appears to be a factor of primary importance in any surgical attempts to treat ascites. For this reason, the primary objective of the studies reported herein was to evaluate the methods of internal drainage of ascites.

At the start of our experimental studies, it became apparent that rigid comparison of human and experimental ascites was not possible because of differences in the mechanisms of formation and composition of the fluid of the two species. Anatomic differences between the abdomen and pelvis of the dog and man also preclude exact evaluation of procedures the use of which has been reported in patients. It was thought, however, that certain useful data might be obtained by comparison of various procedures for internal drainage by experimental studies in dogs.

MATERIALS AND METHODS

Adult mongrel dogs weighing from 20 to 50 pounds have been used. Seventy animals were employed during the course of the experiments. Some of the animals died a short time following operation; others were used to evolve the surgical techniques, and, therefore, had to be excluded from the final group which includes 50 animals.

The method of production of ascites used corresponded basically to that of McKee, Schilling, Tishkoff, and Hyatt. It was standardized to produce 50 to 60 per cent constriction of the thoracic inferior vena cava. A right thoracotomy at the level of the fifth intercostal space was performed under endotracheal intubation and intravenous nembutal anesthesia. The right lung was retracted and the phrenic nerve overlying the inferior cava was dissected free of the vessel for about 4 centimeters midway between the diaphragm and the entry of the vein into the right atrium.

The constricting band was then applied to the inferior vena cava at this level. Vessels less than 15 millimeters in diameter were narrowed with a plain stainless steel ring (measuring approximately 6 millimeters in length), while larger veins were constricted using an 11 millimeter ring containing the water-absorbing casein plastic, ameroid, enclosed within the steel ring. The opening in the smaller ring was closed by application of pliers, while ligatures were applied to the circumference of the ameroid-containing rings. The thoracotomy wound was closed in layers in the usual fashion. Before insertion of the last sutures the lung was re-expanded, all air being expelled through a fine rubber catheter immersed in sterile water, following which the catheter was removed. Detectable ascites developed within 2 to 3 weeks in all survivors except some of those

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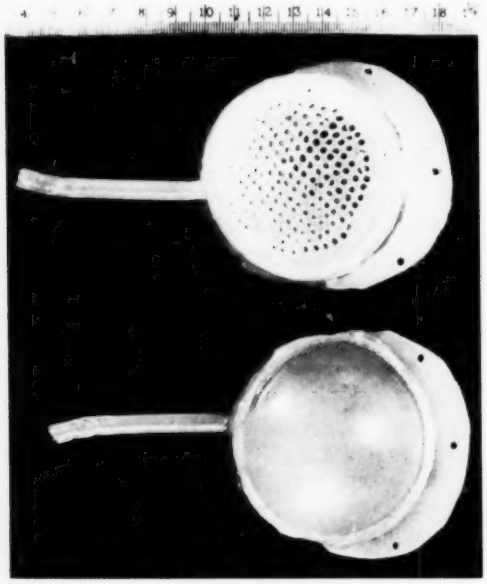

FIG. 1. Anterior and posterior views of polythene prosthesis.

dogs which had the relief procedure at the same time as the chest operation.

The following operations were performed on dogs in an attempt to relieve the ascites:

Group I. Polythene prosthesis in peritoneal cavity with drainage to the exterior—6 dogs. Through a lower abdominal midline incision, omentectomy was performed, and the prosthesis (Fig. 1) was inserted into the abdomen, its periphery being anchored to the anterior parietal peritoneum. The conducting tube was led out through a stab wound in the anterior abdominal wall where it was anchored, with a rubber bag tied to it to collect the draining ascites.

Group II. Prosthesis in peritoneal cavity with drainage to retropubic space: (a) polythene prosthesis—10 dogs; (b) silicone rubber prosthesis—6 dogs. The procedure was carried out as in group I except that the conducting tube was not led to the exterior. Internal drainage was provided to the fatty areolar tissue by attaching the tube extraperitoneally and anterior to the bladder neck, corresponding to the space of Retzius in man. The peritoneum was then closed around the tube.

Both the polythene and silicone rubber prostheses combine the principle of a sieve with multiple perforations through which the ascites is to drain. This sieve is either flat or concave, with a diameter of 7 to 8 centimeters and containing 200 or more perforations. The sieve leads into a chamber 1 to 2 centimeters in depth, and from this the fluid is funneled out through a hollow tube of the same material. Around the periphery of the sieve-collector is a thin rim of plastic or rubber by which the prosthesis is anchored to the parietal peritoneum of the anterior abdominal viscera.

Group III. Omentopexy to retropubic space—15 dogs. Through a lower abdominal incision, the greater omentum was sutured to the extraperitoneal tissues anterior to the bladder neck, around which the peritoneum was closed.

Group IV. Omentopexy followed by splenectomy—4 dogs. Two weeks after omentopexy, routine splenectomy was carried out through a left paramedian incision.

Group V. Omentectomy and ileoexstrophy—9 dogs. Through a long right paramedian incision, omentectomy and exclusion of a segment of terminal ileum about 4 inches long with end-to-end anastomosis of the small intestine was carried out. The excluded segment with its blood supply intact was opened near its antimesenteric border, and the loop was anchored by interrupted silk sutures to the anterior parietal peritoneum, approximating abraded bowel serosa to peritoneum.

It became apparent that the evaluation of the volume of ascites by weighing the animals and measurements of abdominal circumference was not sufficiently accurate to permit careful analysis of the value of each procedure.

It was decided, therefore, to use the diazo-dye, Evans blue, as a labelling substance to measure the volume of ascites and also the rate of absorption of ascitic fluid. Samples of blood and ascitic fluid were

drawn from the lightly anesthetized dogs, and 40 to 75 milligrams of Evans blue dye were injected into the peritoneal cavity. Samples of blood and ascitic fluid were removed at half-hour intervals for 2 hours, the weights of the animals were recorded and hematocrit readings were determined. At the end of 2 hours, 10 milligrams of dye were injected intravenously, and blood samples were taken at 10 and 20 minutes after injection. The T-1824 concentration was determined from the optical density by using a K (calibration constant) value after the method of Gibson and Evelyn. Simple arithmetical calculations provided blood and plasma volumes, ascitic fluid volumes, and volume of ascites absorbed per pound of body weight per hour.

RESULTS

Group I. Of the 6 dogs used, 4 died within 4 days after the external drainage procedure carried out 2 weeks after constriction of the thoracic inferior vena cava. The 2 remaining animals survived for 8 and 9 days respectively, maintained on daily intravenous fluids and electrolytes.

Drainage to the exterior was effective for the short period of time which these dogs survived postoperatively. Most of the drainage was around the tube, however, while the peritoneal cavity at autopsy and the collecting bags contained little fluid.

Group II. The dogs survived longer after drainage to the prevesical space. Three of the 10 animals into which the polythene prosthesis was inserted died within 1 week, 4 survived 1 to 2 weeks, while 3 lived for longer than 2 weeks, 1 surviving 23 days after operation. All those dogs which lived for more than 2 weeks with the polythene in place showed only minimal ascites.

Only 2 out of 6 dogs into which the silicone rubber prosthesis was implanted survived longer than 2 weeks; both of these animals showed massive volumes of ascites at autopsy.

Group III. In 15 dogs the omentum was fixed to the prevesical space extraperitoneally. Twelve animals were subjected to thoracic inferior vena cava constriction at the same time as omentopexy, while in 3 dogs omentopexy was performed about 2 weeks after the thoracic procedure.

A total of 12 animals survived longer than 2 weeks after omentopexy to the retropubic region. Of these, 9 had ascites, while 3 did not. Three of those which had abdominal accumulations had only a small volume of ascites. One dog with ascites also had a pleural effusion at autopsy. In 2 dogs, ascites persisted for 130 and 150 days, respectively.

Group IV. As mentioned, 4 dogs which had undergone retropubic omentopexy were splenectomized about 2 weeks later. All had ascites at the time of splenectomy. Two of this small series showed minimal ascites at autopsy. The other 2 became eviscerated postoperatively and required sacrifice.

Group V. Only 3 of the 9 dogs which were subjected to omentectomy and ileoexstrophy survived longer than 2 weeks. One showed a small volume of fluid at autopsy, while the other 2 had large volumes of ascites. Pathologic examination of the everted loop and adjacent serosa may explain our results. Only in that dog which survived 60 days was the segment adherent to peritoneum throughout its length; minimal ascites was present in this dog.

COMMENTS

Animals of group I, in which external drainage was carried out, as mentioned previously, survived only for short periods of time. Those given parenteral therapy lived somewhat longer. It was evident that continuous external drainage resulted in loss of protein, fluid, and electrolytes, to which the animals succumbed. Mulvany and Ferguson have drained ascites via the urinary tract in human beings, and did not report protein and electrolyte deficiencies. Incomplete drainage of the ascites may have been present, however, with sufficient fluid remaining within the abdomen to permit the maintenance of fluid and salt balance and the prevention of protein deficiencies.

Our experience with our prosthesis (group II) was somewhat disappointing. A device with multiple perforations was constructed in an attempt to avoid fibrin-plugging for a longer time. In addition, the conducting tube would create a fistula by which fluid might pass into the retropubic space even after the perforations had sealed. In our dogs, at least half of the perforations became plugged with fibrin. In addition, many of the prostheses and conducting tubes contained a clot at the time of autopsy, despite the use of silicone-coating, injections of parenzymol, and the nonwetting characteristics of silicone rubber. Furthermore, the tip of the tube excited a granulomatous reaction in the surrounding tissue, which probably would have healed by fibrosis with longer survival.

The prosthesis should not be abandoned before adequate tests of its value in man. The important feature to appreciate from animal use is the relative harmlessness of the device. The mild pressure effects observed will be overcome probably by differences in anatomy between the dog and man and by altering its size and shape in such a way as to conform to the requirements of the human pelvis.

Animals of group III in which omentopexy to the retropubic region was carried out survived longer, as previously mentioned, than after any other operative procedure. In dogs in which the omentopexy was carried out at the same time as constriction of the thoracic inferior vena cava, the volume of the subsequent ascites was considerably reduced in 50 per cent of the animals. In cases in which the volume of ascites was not diminished following fixation of the omentum to the retropubic space failure of fusion of the omentum and retropubic fat was observed.

In human subjects, omentopexy into the space of Retzius as a means of improving collateral circulation has had extensive modifications. From anatomic studies, Kopf noted that the retropubic space of Retzius possesses a rich venous and lymphatic plexus which could be used to establish improved collateral circulation. He anchored the omentum in the prevesical space extraperitoneally as far down as the bladder neck, with improvement in 2 cases of cardiac ascites. Both Kolb and Lorbek and Steinhardt and Saexinger have drained the peritoneal cavity through a palladon button to the space of Retzius. The majority of their patients died within 6 weeks postoperatively, but survivors showed marked improvement. It appears that this procedure is of definite value in some cases of ascites and should be used more extensively, so that a larger series of cases may be evaluated.

The value of splenectomy in alleviating ascites would appear to arise from the resulting decrease in inflow to the portal venous system. About 50 per cent of all patients treated in this manner improve, although the development of collaterals in time restores the net portal blood flow with reaccumulation of fluid in many cases. In our studies, the group in which splenectomy was carried out comprised 4 dogs only, and is therefore too small from which to derive any conclusions. In 2 of these dogs, the ascitic volume was considerably diminished. In the other 2 dogs, the value cannot be ascertained since both of them eviscerated postoperatively for other causes. It is intended to study a larger number of animals by using this procedure. The impression of the authors is that the value of splenectomy in surgical relief of ascites has been underestimated in the past.

In the few animals which survived sufficiently long to evaluate the effects of omentectomy and ileoexstrophy, the volume of intraperitoneal fluid was not markedly diminished. Chronic ileitis was present in this loop and comparison with cases of chronic enteritis in human beings raises the question as to whether this loop could function adequately. New vessels in the scar tissue may serve as a source of collateral circulation with, therefore, less formation of ascites rather than increased absorption through the mucosa. In other specimens

there was adherence only near points of suture, with fibrinous and cellular deposition separating serosa and peritoneum. Continuous bathing by fluid may prevent adhesion of bowel and parietes before individual organization of the fibrin layers occurs, with failure of the operation.

By excluding a loop of ileum and attaching its serosa to the parietal peritoneum, thus exposing its mucosa to the peritoneal cavity, Neumann and associates have improved cirrhotic ascites. A 50 per cent postoperative mortality due to complications of the underlying disease occurred, imposing limitations on the use of the procedure.

The volumes of ascites absorbed per hour per pound of body weight are not amenable to statistical analysis as the same dog absorbs at different rates at different times. In addition, the depth of anesthesia affects the rate of absorption and it probably was not exactly the same for each observation. Insufficient control and postoperative studies were carried out on each dog to allow for averages and evaluation of results. Further refinements of our techniques are also necessary, namely precise measurement of volume of dye injected, control of depth of anesthesia which affects the rate of respiration and lymph flow, determination of the rate of disappearance of Evans blue from the circulation, and the use of a colorimeter which gives accurate readings at very high dye dilutions. The determination of rates of absorption of ascites before and after ameliorative surgery by means of Evans blue is recommended, however, provided cognizance is taken of the variables mentioned.

Before applying or rejecting the experimental procedures used in this study, one must be satisfied that the mechanisms of ascites formation in human beings are comparable to the conditions used in the laboratory. Inferior vena cava constriction with hepatic congestion appears analogous to ascites secondary to congestive heart failure, constrictive pericarditis, the Budd-Chiari syndrome, and cirrhosis in which there is outflow blockage to the hepatic venous system. The ascites secondary to carcinomatosis, peritonitis, nephritis, and nephrosis, however, requires the implication of other factors. It appears that some of the procedures employed in our experiments, particularly the use of a prosthesis, might be advantageous in inoperable cancer patients.

A second problem is related to the characteristics of experimental ascites. Human ascites, unless of extremely high protein content, does not coagulate. Most of our samples clotted in vitro, while many showed evidence of coagulation in vivo when the prosthesis was used. A difference in the physicochemical properties of ascites between the two species seems to exist, thus perhaps overcoming one of the difficulties encountered in the employment of the prosthesis.

Although similar morphologically, the prevesical space may exhibit some functional differences between dog and man. The space of Retzius in the human being may be more active in absorbing ascites. Trials of drainage to this region should be pursued further.

SUMMARY

An experimental evaluation of various methods of surgical amelioration of ascites carried out on 70 dogs is reported.

The following groups have been studied: (1) polythene prosthesis draining from the peritoneal cavity to the exterior; (2) prostheses draining from the peritoneal cavity to the retropubic space—polythene or silicone rubber; (3) omentopexy to the prevesical region; (4) Retzius space omentopexy followed 2 weeks later by splenectomy; (5) omentectomy and ileoexstrophy.

Evans blue dye has been used to estimate the volume of ascites after corrective procedures.

Although none of the methods employed proved to be completely satisfactory, it appears that methods of internal drainage of ascites by the use of the space of Retzius seem to be the most promising ones. Evaluation of the effects of splenectomy appears to

warrant a trial on a larger group of animals. Over 50 per cent of patients with chronic ascites do not respond to medical management, a group sufficiently large to encourage further studies of surgical methods of relief.

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MYOCARDIAL FUNCTION AFTER ELECTIVE CARDIAC ARREST DURING HYPOTHERMIA

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IT HAS BEEN DEMONSTRATED previously (4) that prolonged cardiac arrest by potassium citrate causes severe depression of myocardial function in the dog. Clinical and laboratory experience suggests that hypothermia provides a protective effect against certain complications of elective cardiac arrest. We have investigated left ventricular function in hypothermic dogs after elective cardioplegia with potassium citrate and have demonstrated that hypothermia affords partial protection from the untoward effects of such prolonged periods of cardiac arrest.

METHODS

Mongrel dogs of 8.5 to 11.0 kilograms of body weight were used. Light anesthesia was introduced by thiopental sodium intravenously, and subsequent immobilization was achieved by intravenous use of succinyl choline (0.1 per cent). Pulmonary ventilation was maintained by a mechanical respirator which delivered 100 per cent oxygen through an endotracheal tube at a pressure of 15 to 20 centimeters of water. Esophageal temperature was recorded by a thermistor probe.

Arterial blood pressure was measured through a catheter inserted in the femoral artery by means of a P23A Statham pressure transducer. A carotid artery was catheterized to permit sampling of arterial blood for dye analysis. A jugular vein was catheterized to permit rapid transfusion. Following right thoracotomy, a short polyethylene catheter (PE-60) was inserted into the right atrium by way of the azygos vein as a conduit for rapid injection of dye. The left atrium was catheterized by way of a pulmonary vein for recording of left atrial pressure by means of a water manometer. Cardiac output was measured by the indicator dilution technique utilizing indocyanine green and a cuvette densitometer. Arterial pressure and lead II of the electrocardiogram were recorded on a direct writing oscillograph. Indicator dilution curves were recorded on a direct writing milliammeter.

Ventricular function curves were constructed by plotting calculated stroke work at various left atrial pressures (filling pressures) in response to transfusion of whole blood:

$$\text{Left ventricular stroke work in gram-meters} = \frac{\text{Stroke volume in c.c.} \times \text{mean arterial blood pressure} - \text{mean left atrial pressure in cm. } H_2O}{100}$$

Peripheral resistance was calculated by the method described by Green and his associates.

After obtaining the necessary measurements for the construction of a left ventricular function curve at normal body temperature (36 to 37 degrees C.), the animal was cooled to between 27 and 30 degrees C. Left ventricular function was again assessed. The right atrium and femoral artery were cannulated. Heparin (2.5 mgm./kgm.) was given intravenously and cardiopulmonary bypass was instituted. Extracorporeal oxygenation was accomplished with a stainless steel rotating disc oxygenator. Mean arterial pressure was maintained between 100

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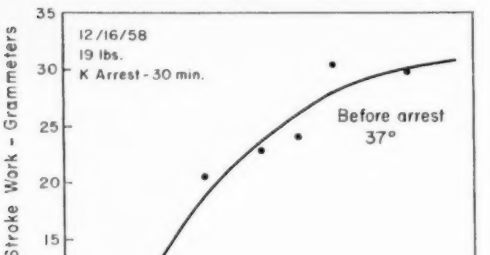

FIG. 1.

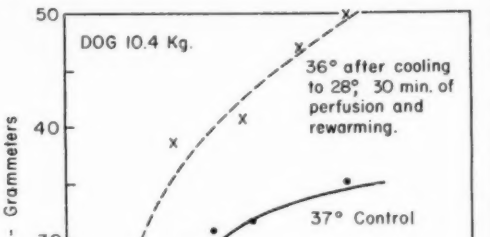
DOG 10.4 Kg.
36° after cooling to 28°, 30 min. of perfusion and rewarming.
37° Control
Left Ventricular Stroke Work - Grammeters
Mean Left Atrial Pressure - Cm. of H_2O

FIG. 2.

FIG. 1. Left ventricular function curves before and after 30 minutes of elective cardiac arrest with potassium citrate at normal body temperature.

FIG. 2. Left ventricular function curves before and after cooling dog to body temperature of 28 degrees C., 30 minutes of cardiopulmonary bypass at 28 degrees C., and rewarming to 36 degrees C.

and 125 millimeters of mercury during cardiopulmonary bypass. Cardiac arrest was induced with 2.5 per cent potassium citrate in whole blood in the usual manner. To prevent cardiac overdistention and engorgement of the lungs, the left side of the heart was decompressed.

After 30 minutes, the aortic clamp was removed, and cardiac action was reinstituted. Ventricular defibrillation, when necessary, was accomplished by electroshock. Ten to 30 minutes after the animal was able to support his circulation without aid from the pump-oxygenator circuit, ventricular function was re-evaluated. The animal was then rewarmed to 35 to 37 degrees C., and ventricular function was restudied.

RESULTS AND DISCUSSION

Control experiments. Figure 1 demonstrates the depression of left ventricular stroke work which follows 30 minutes of potassium arrest at 37 degrees C. It has been previously shown that surgical manipulation and cardiopulmonary bypass of themselves do not contribute appreciably to this depression and that this depression occurs in the presence of "adequate" arterial blood pressure, a "normal" heart rate, and a satisfactory electrocardiogram.

In order to evaluate whether cooling, cardiopulmonary bypass, and rewarming would affect ventricular function, experiments were carried out which excluded the 30 minute period of cardioplegia. The empty heart was allowed to beat for 30 minutes at a body temperature of 28 degrees C. while coronary oxygenation was provided by an extracorporeal oxygenating system. Figure 2 shows no impairment, probably slight improvement in this instance, in the stroke work ability of the left ventricle at the end of the procedure. Total work values were essentially the same before and after the procedure. This confirms the report of McMillan and his colleagues that the procedure of cooling and

rewarming the canine heart does not alter its ventricular function curve. A decline in total left ventricular work during hypothermia as reported by Edwards and his colleagues was noted.

Potassium citrate arrest during hypothermia. Six dogs were subjected to 30 minutes of cardiac arrest with potassium citrate during cardiopulmonary bypass at 27 to 30 degrees C. The data from one such experiment are shown in Figure 3 which is representative of the group. After the animal had been rewarmed to 37 degrees C., the depression in stroke work ability was obvious. It is interesting that this depression was not evident or was less than controls if the animal remained hypothermic in the period after arrest. The benefit which hypothermia affords these "failing" canine hearts may be explained by the increased tolerance of the canine heart to hypoxia during hypothermia and the more rapid extrusion of the potassium ion from the intracellular compartment of the heart during hypothermia.

Myocardial depression was unmistakable after rewarming. However, if one compares the severity of this depression with the severity of the depression which occurs in animals of the same size arrested at normal temperatures (Fig. 1), one is impressed that there has been significant protection from the untoward effects of the arrest. It was of interest that none of the dogs which underwent cardiac arrest at 37 degrees were able to do more than 8 (usually under 7.0) grammeters of work at any filling pressure. In contrast, all animals cooled before arrest and rewarmed after arrest were able to exceed 15 grammeters of work on demand. Lower levels of hypothermia might well offer greater protection.

This study emphasizes the advantage of measuring cardiac output and stroke work as well as blood pressure and heart rate in evaluation of the patients after cardiac operations. Examination of the data (Fig. 3) shows that impaired stroke volume is the main determinant of the depressed stroke work values. As would be expected, the

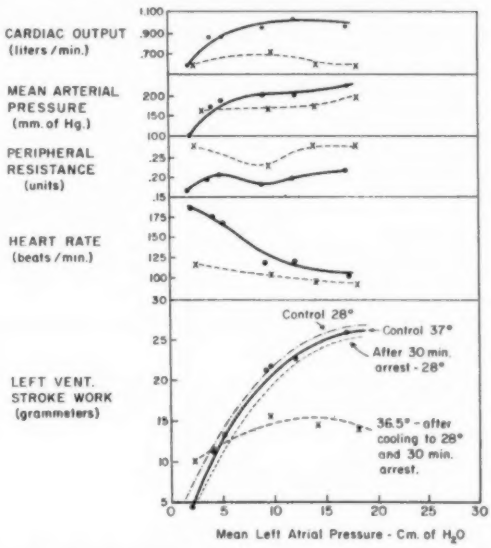
CARDIAC OUTPUT (liters / min.)
MEAN ARTERIAL PRESSURE (mm. of Hg.)
PERIPHERAL RESISTANCE (units)
HEART RATE (beats / min.)
LEFT VENT. STROKE WORK (grammeters)
Control 28°
Control 37°
After 30 min. arrest - 28°
36.5° - after cooling to 28° and 30 min. arrest.
Mean Left Atrial Pressure - Cm. of H2O

FIG. 3. Hemodynamic responses before and after cooling dog to 28 degrees C. 30 minutes of elective cardiac arrest with potassium citrate, and rewarming to 36.5 degrees C. Dog weight is 9.0 kilograms.

blood pressure is being maintained at a normal range by vasoconstriction, as shown by increase in calculated total peripheral resistance. The trial by transfusion clearly excludes diminished blood volume as the cause of low cardiac output.

The results support the concept that primary myocardial weakness or failure may contribute significantly to the postoperative morbidity and mortality in those patients who undergo elective chemical cardiac arrest.

SUMMARY

We have studied left ventricular function of dogs which underwent elective cardiac arrest under hypothermia (28 to 30 degrees C.) in comparison to left ventricular function of dogs which were similarly tested at 37 degrees C.

Left ventricular function curves were constructed from measurements which were obtained of cardiac output, heart rate, mean arterial blood pressure, and mean left atrial pressures.

The canine heart arrested with potassium citrate at 28 degrees C. is able to perform more than 15 grammeters of stroke work in response to trial transfusion after the arrest. In contrast, the heart of a dog of comparable size which is arrested at 37 degrees C. is unable to exceed 8 grammeters of stroke work during the period following arrest.

These results indicate that hypothermia offers partial protection to the canine myocardium subjected to 30 minutes of arrest with potasium citrate.

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COMPARISON OF THE RECOVERY FROM METHOHEXITAL AND THIOPENTAL ANESTHESIA IN MAN

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THE INDUCTION of anesthesia by intravenous thiobarbiturates is unquestionably most acceptable to the patient. Consciousness is lost quickly and pleasantly without the need to tolerate a face mask or inhale a malodorous anesthetic. Recovery from anesthesia is often smoother, and again from the patient's point of view usually more acceptable, than with the inhalational anesthetic agents. These factors and the impression that the thiobarbiturates are "ultra short-acting" have led to their choice for anesthesia for out-patient surgery. Actually, rapid recovery from thiobarbiturate anesthesia is caused by distribution of the drug in body tissue and by the affinity of fat for thiobarbiturates. Both mechanisms lower the concentration in the blood. Detoxification occurs slowly, and appreciable blood levels may persist for more than 24 hours. For this reason, out-patients experience dizziness, lack of co-ordination, and mental confusion if discharged from the hospital or doctor's office too soon after thiobarbiturate anesthesia. Hence, a more rapidly detoxified barbiturate would be advantageous for out-patient work.

Gruber, Stoelting, Forney, White, and DeMeyer and Gibson, Swanson, and Doran have reported on an oxybarbiturate, No. 22451, which is rapidly detoxified and, therefore, produces hypnosis of shorter duration than thiopental. Unfortunately, a high incidence of convulsive-like movements was observed. Subsequently, the high boiling point isomer of No. 22451, methohexital (No. 25398) was shown to have a similar detoxification pattern and to give satisfactory anesthesia. Theoretically, the period of recovery and "hangover" should be shorter following methohexital than after thiopental. If this is true, methohexital would be the preferable anesthetic for out-patient surgery. In this study, we have compared the duration of the loss of consciousness and return to a reasonably normal state after approximately equipotent doses of the two drugs.

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METHOD

A complex reaction timer was obtained from the American Automobile Association. This instrument estimates quantitatively the ability of a subject to perform the tasks of driving a car by recording in milliseconds the time required to turn a wheel or apply the brake after an appropriate signal. It is sensitive to changes in mood and ability to concentrate; for example, the reaction time of a subject will be increased after a sleepless night.

Fourteen healthy subjects were studied. Hypnosis was produced by the intravenous injection of 1 per cent methohexital or 2.5 per cent thiopental. One milliliter of solution was given every 5 seconds until the subject would cease to count or respond to command. On other occasions the subjects received twice the hypnotic dose of the respective drugs at the rate of 2 milliliters every 5 seconds. Each subject was studied 4 times with minimum intervals of 1 week. Before the study, the subject was tested with the complex reaction timer. Blood pressure was obtained by auscultation with a mercury manometer before and immediately after the injection of the drugs and during the "driving" period when the subject sat

TABLE I.—DURATION OF SLEEP AND RECOVERY AFTER HYPNOTIC DOSES OF BARBITURATES

	Thiopental			*Methohexital*		
Subject	*Dose, mgm.*	*Time count, seconds*	*Time recover, seconds*	*Dose, mgm.*	*Time count, seconds*	*Time recover, seconds*
C.W. 23WM 72″ 168#	300	140	575	100	200	370
P.M. 20WM 68″ 164#	250	155	960	90	205	650
J.B. 33WM 71″ 160#	300	75	1060	70	140	720
S.P. 29WM 76″ 280#	300	135	765	100	130	820
B.C. 45WM 68″ 175#	250	120	1215	75	125	910
H.T. 27WM 70″ 195#	250	510	1410	110	210	1590
E.P. 30WM 70″ 150#	275	115	1320	110	180	955
W.M. 21WM 73″ 150#	250	180	1145	100	130	750
S.D. 28WM 69″ 170#	250	1150	2915	100	195	840
N.G. 33WM 73″ 150#	250	95	275	95	140	505
R.P. 43WM 71″ 200#	250	120	1095	100	145	480
U.S. 21WF 68″ 131#	225	155	1310	90	245	1445
D.E. 23WF 62″ 97#	200	65	2720	80	140	1305
M.G. 31WF 64″ 132#	200	220	1005	70	210	635
Mean	253	231	1268	92	179	854

upright. Analysis was made of differences between the groups in: (1) duration of unconsciousness; (2) the time necessary to recover sufficiently to "drive" normally; and, (3) the incidence of side effects.

RESULTS

The average dose of methohexital producing hypnosis was 92 milligrams while that for thiopental was 253 milligrams (Table I). The duration of unconsciousness was not significantly shorter after methohexital (average 179 seconds) than after thiopental (average 231 seconds). However, the time of complete recovery, i.e., when the subjects had returned to control reaction times, was shorter ($P<.05$) for methohexital (854 seconds) than for thiopental (1,268 seconds). After the larger doses of the two hypnotics (Table II), recovery of consciousness as well as the ability to drive was significantly shorter with methohexital ($P<.01$). Most subjects, while appearing objectively normal during the latter part of the recovery period, reported fatiguability, forgetfulness, and the impression of compression of time so that time passed unusually rapidly. The subjects also stated they experienced less "hangover" and were mentally clearer after methohexital. In every case in which subjective effects of the barbiturate persisted in the absence of objective effects, the complex reaction timer confirmed this fact. In several instances when the subjects judged themselves to be completely recovered, the timer revealed that their reaction times were not back to normal.

A slight decrease in blood pressure occurred after the injection of both drugs. Hypotension to 80/60 millimeters of mer-

TABLE II.—DURATION OF SLEEP AND RECOVERY AFTER DOUBLE DOSES OF BARBITURATES

	Thiopental			*Methohexital*		
Subject	*Dose, mg.*	*Time count, seconds*	*Time recover, seconds*	*Dose, mgm.*	*Time count, seconds*	*Time recover, seconds*
C.W.	600	2430	3900	200	775	2290
P.M.	500	1960	3840	200	570	900
J.B.	600	790	4620	150	245	2260
S.P.	600	590	5405	200	345	975
B.G.	500	485	2790	150	285	1550
H.T.	500	1515	3510	220	1035	3360
E.P.	550	375	4890	220	295	3015
W.M.	500	1910	3980	200	375	1590
S.D.	500	1890	4800	200	1055	2205
N.G.	500	240	1755	190	350	990
U.S.	450	1355	4270	190	395	2400
D.E.	400	345	3360	160	275	3585
M.G.	400	1830	3720	140	390	950
Mean	508	1210	3910	186	492	1930

cury was noted in 2 subjects while sitting at the reaction timer. Both had to lie down intermittently during recovery until the blood pressure stabilized. This occurred after 250 milligrams of thiopental (subject R. P.) and after 190 milligrams of methohexital (subject N. G.).

Side effects were noted more frequently after methohexital (Table III). Motor movements, consisting of fibrillation around the eyes and mouth, and in 1 individual generalized muscular twitching occurred after methohexital. These movements subsided within 2 to 3 minutes. Motor movements following thiopental seemed associated with the withdrawal of the needle from the vein, seen only in light hypnosis with the smaller dose.

DISCUSSION

To our knowledge, the complex reaction timer has not been used previously to evaluate recovery from anesthesia. Drew, Colquhoun, and Long found a similar instrument reasonably sensitive investigating the disability following ingestion of alcohol. We have found the complex reaction timer a worthwhile instrument sensitive not only to drug induced changes but also to the inability of the subject to concentrate because of distracting noises or talk. Several of our subjects considered themselves able to drive safely before their reaction time had returned to normal.

Our data support those of previous reports indicating that methohexital is about 2½ times as potent as thiopental with a comparative duration of effect approximately two-thirds as long. Methohexital, like its isomer No. 22451 is probably detoxified more rapidly than thiopental. This would be an advantage for anesthesia in outpatients.

Our experience indicates that motor disturbances are more likely to occur with methohexital. Redish, Vore, Chernish, and Gruber reported 1 patient with abnormal motor activity and with a convulsive electroencephalographic pattern during anesthesia with methohexital. Their other patients did not exhibit this phenomenon. Wyant, Dobkin, and Aasheim reported that anesthesia

TABLE III.—INCIDENCE OF SIDE EFFECTS

	Thiopental		*Methohexital*	
	1. Hypnotic dose	*2. Double dose*	*3. Hypnotic dose*	*4. Double dose*
Apnea	4	9	2	8
Cough	1	1	0	2
Hiccoughs	0	1	1	5
Numbness—tingling	2	3	0	0
Twitch	0	2	5	6
Total No. of studies	13	13	13	13

Apnea: Columns 2 and 4 compared to columns 1 and 3, Significant $P<.01$.
Twitch: Columns 3 and 4 compared to columns 1 and 2, Significant $P<.050$.

with methohexital was the least satisfactory of 7 intravenous anesthetics tested, because of associated movements. In a double blind study, Eckenhoff and Norton found a 14.4 per cent incidence of muscular movement and tremors associated with methohexital anesthesia as compared to a 6.0 per cent incidence with thiopental. Other reports have failed to observe this complication. Methohexital may be useful with succinylcholine in the management of electroshock therapy.

The occurrence of hypotension following intravenous barbiturate anesthesia deserves emphasis. Early ambulation during recovery should be with caution.

The search among the oxybarbiturates for an intravenous agent of short duration with less cumulation than thiopental should be continued, since in our opinion the complication of muscle fasciculation will probably preclude the widespread acceptance of methohexital.

SUMMARY

A new oxybarbiturate, methohexital, was compared for duration of effect with thiopental in 14 subjects using a complex reaction timer. Methohexital produced hypnosis lasting approximately two-thirds as long as equivalent doses of thiopental. The complete recovery from methohexital was approximately twice as rapid as from thiopental. However, methohexital hypnosis was associated with a significantly higher incidence of motor movements than was thiopental.

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THE ROLE OF THE LACK OF OXYGEN IN IRREVERSIBLE CARDIAC ARREST

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RECENT STUDIES reported from this laboratory demonstrated that an isolated, perfused guinea pig heart arrested for periods up to 60 minutes by completely occluding the perfusion inflow returned to 82 per cent of its original amplitude of contraction when perfusion was reinstituted. Garb and associates showed that the addition of glucose to substrate-depleted, isolated, perfused mammalian hearts which had failed led to an increase in contractile force. Penna and associates studied the effects of the lack of glucose on the electrogram of the isolated, perfused guinea pig heart. They noted: (1) an increase of PR interval; (2) auriculoventricular dissociation; (3) ventricular fibrillation; and (4) decrease of the voltage of the atrial and ventricular complexes during perfusion without glucose. Ventricular fibrillation induced by the lack of glucose was reversed to normal or idioventricular rhythm by perfusing with glucose.

The observation that guinea pig hearts could be arrested for varying periods when deprived of both oxygen and substrate and would return to 82 per cent of control contractile force and to a control form of electrocardiogram when reperfused with oxygenated Ringer-Locke solution led to investigation of the importance of substrate (dextrose) and oxygen in achieving arrest and in obtaining maximum recovery after arrest. The studies herein reported were done: (1) to evaluate the action of oxygen-free and substrate (dextrose)-free perfusion fluids in producing elective cardiac arrest and the residual effect these solutions might have on recovery; and (2) to compare these results with those obtained in hearts arrested by complete cessation of flow of perfusion fluid. The results obtained in this study may be of significant clinical importance in regard to the occurrence of undesired cardiac arrest during surgery.

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Aided by a grant from the John Polachek Foundation for Medical Research.

MATERIALS AND METHODS

Adult guinea pigs of both sexes with an average weight of 600 grams were anesthetized with sodium pentobarbital, 30 milligrams per kilogram, intraperitoneally. In most cases a small amount of ether was required as a supplement. The heart was removed and inserted into the perfusion apparatus as described in a previous report (3). Two separate reservoirs and oxygenating tubes were connected to the warming spiral with a three-way connector. One Mariotte bottle contained a dextrose-free Ringer's solution consisting of: sodium chloride, 7 grams per liter; sodium bicarbonate, 2.1 grams per liter; potassium chloride, 0.42 gram per liter; calcium chloride, 0.24 gram per liter; and magnesium chloride, 0.2 gram per liter. The other contained Ringer's solution with dextrose 1.8 grams per liter added. The perfusion fluid could flow downward through the meter-long oxygenation tube, while a gas mixture of 95 per cent oxygen and 5 per cent carbon dioxide, in the form of tiny bubbles, could rise from a sintered glass disc at the bottom of the tube. In the group of experiments in which the lack of substrate was studied, oxygenated Ringer's solution was allowed to perfuse the heart until arrest occurred. As soon as this happened, this fluid was stopped and perfusion with oxygenated Ringer's solution with dex-

TABLE I.—EFFECT OF SUBSTRATE AND OXYGEN LACK ON MECHANICAL ACTIVITY

Perfusion fluid (Ringer's sol.)	*No. of determinations*	*Initial (Average)* *Amplit., (cm.)*	*Rate (per min.)*	*Time* to arrest*	*Duration of arrest*	*Time to recovery* *Initial*	*Maximum*	*Maximum recovery* *Amplit. (per cent of initial)*	*Rate (per min.)*	*Duration of reperfusion*
Oxygenated without dextrose.....	6	3.6 (2.3–5.6)	195 (180–212)	47 min. (23–84)	0	11 min. (2–16)	23 min. (2–36)	23 (9–56)	164 (92–192)	63 min. (39–83)
Unoxygenated with dextrose.....	9	2.8 (2.1–4.1)	176 (156–204)	69 min. (29–201)	0 (except 1 case of 13 min.)	6—No recovery 1—34 min. 1—14 min. 1—11 min.	 —48 min. —14 min. —48 min.	0 31.2 1.0 7.4	0 156 Fibrillation 132	53 min. (15–135)
Unoxygenated without dextrose.....	8	2.5 (1.7–3.8)	179 (144–208)	49 min. (17–122)	0	5—No recovery 1—16 min. 1— 9 min. 1— 8 min.	 —42 min. —22 min. —43 min.	0 19.0 32.0 28.9	0 164 180 144	57 min. (10–130)
Cessation of perfusion fluid.....	10	2.0 (1.0–3.1)	192 (180–210)	5 min. 8 sec. (3½–10)	22 min. 1 sec. (1–60 min.)	47 sec. (8 sec.–2 min. 35 sec.)	5 min. 51 sec. (1 min. 45 sec.–8 min.)	82.4 (68–92)	205 (196–200)	45 min. (5–100)

*All times listed are average.
Figures in parentheses represent the range of variation.

trose was begun. The group of hearts in which lack of oxygen was evaluated were perfused with unoxygenated Ringer's solution with dextrose until arrest occurred, after which oxygenated Ringer's solution with dextrose was begun. A third group of hearts was perfused with an unoxygenated Ringer's solution without dextrose until arrest occurred, and then perfusion with oxygenated Ringer's solution with dextrose was instituted. In a fourth group, after suitable control tracings had been obtained using oxygenated Ringer's solution with dextrose, the perfusion was stopped until arrest occurred, after which perfusion with oxygenated Ringer's solution with dextrose was restarted. In this group, also some hearts which became arrested mechanically were not reperfused in order to determine how long after mechanical arrest, electrical arrest occurred. The four groups evaluated were: (1) those perfused with Ringer's solution with oxygen but without substrate (dextrose); (2) those perfused with Ringer's solution with substrate (dextrose) but without oxygen; (3) those perfused with Ringer's solution without dextrose and without oxygen; (4) those in which there was complete cessation of perfusion. Contractile force and heart rate were recorded by means of a suitable writing lever. Lead II electrocardiograms were registered using 3 stainless steel wire electrodes placed through the right and left auricular appendages and the apex.

A different heart was used for each determination. The times to achieve mechanical and electrical arrest and recovery were noted. The contractile forces, as determined by the amplitude of contraction before the test perfusion and after maximum recovery, were obtained by direct measurements from the records. Temperature of the warming spiral and the chamber was maintained at 38 ± 0.5 degrees C. in each instance.

RESULTS (SEE TABLE I)

Perfusion with oxygenated Ringer's solution without dextrose. In 6 determinations, the average initial amplitude of contraction (control) was 3.6 centimeters with an average heart rate of 195 beats per minute. Arrest occurred after an average of 47 minutes of perfusion. Immediately upon achieving mechanical arrest, substrate-free

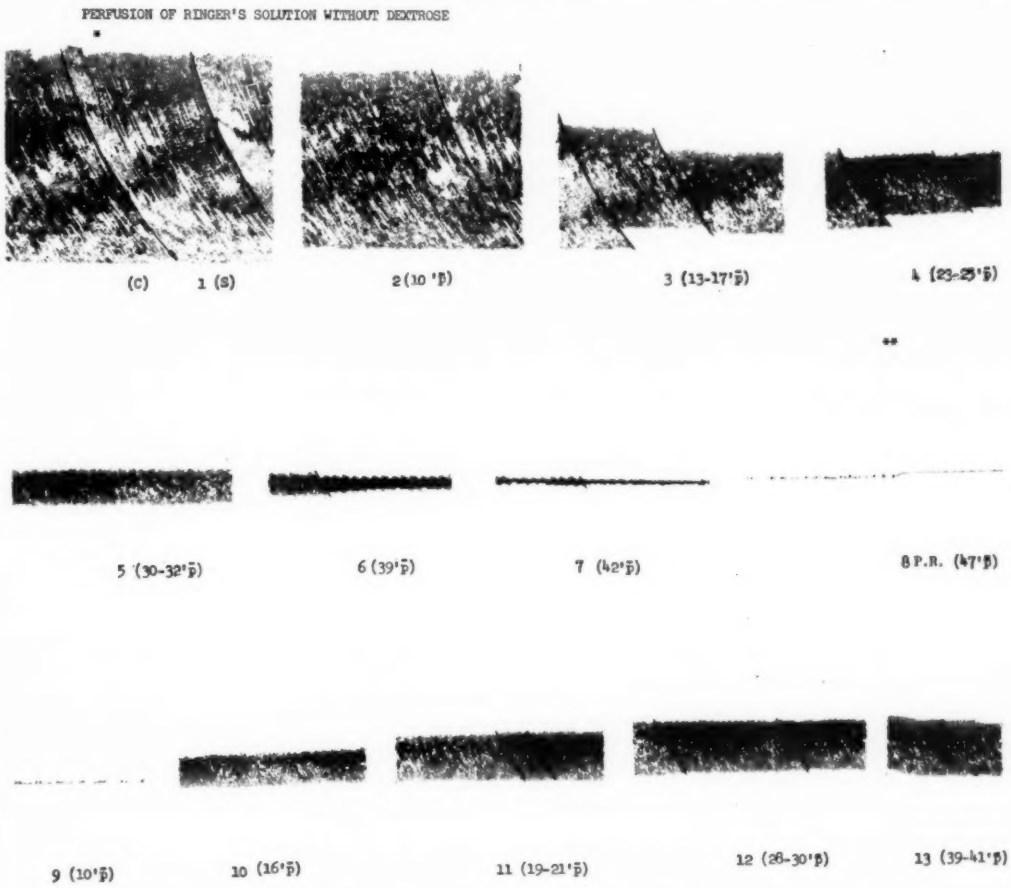

FIG. 1. Recording of amplitude of contraction during perfusion with oxygenated Ringer's solution without dextrose. Control contractile force is indicated by (*C*) in *1*. At (*S*) perfusion with oxygenated Ringer's solution without dextrose was started. Sections *2*, *3*, *4*, *5*, *6*, *7*, and *8* represent contractile forces at the times after perfusion with the test fluid as noted. At ** perfusion with oxygenated Ringer's solution with dextrose was begun, 47 minutes after perfusion with substrate-free fluid was initiated. Sections *9*, *10*, *11*, and *12* represent contractile forces at the times indicated. At *13*, 39 to 41 minutes after perfusion was restarted, maximum recovery of 28 per cent of initial amplitude of contraction was achieved.

solution was stopped and perfusion with Ringer's solution containing dextrose was begun. Initial recovery occurred after an average of 11 minutes, while maximum recovery was achieved at an average of 23 minutes. The average maximum amplitude of contraction reached after recovery was 23 per cent of the initial amplitude, with a range of 9 to 56 per cent. Heart rate at the time of maximum recovery averaged 164 beats per minute, with a range of 92 to 192 beats per minute. The hearts were reperfused for periods of 39 to 83 minutes, the average being 63 minutes (Fig. 1).

Electrocardiograms were done in 5 instances. The change noted was chiefly a decrease in voltage (amplitude) of atrial and ventricular complexes, and in some cases there was a slight decrease in rate. Fibrillation of atria or ventricles did not oc-

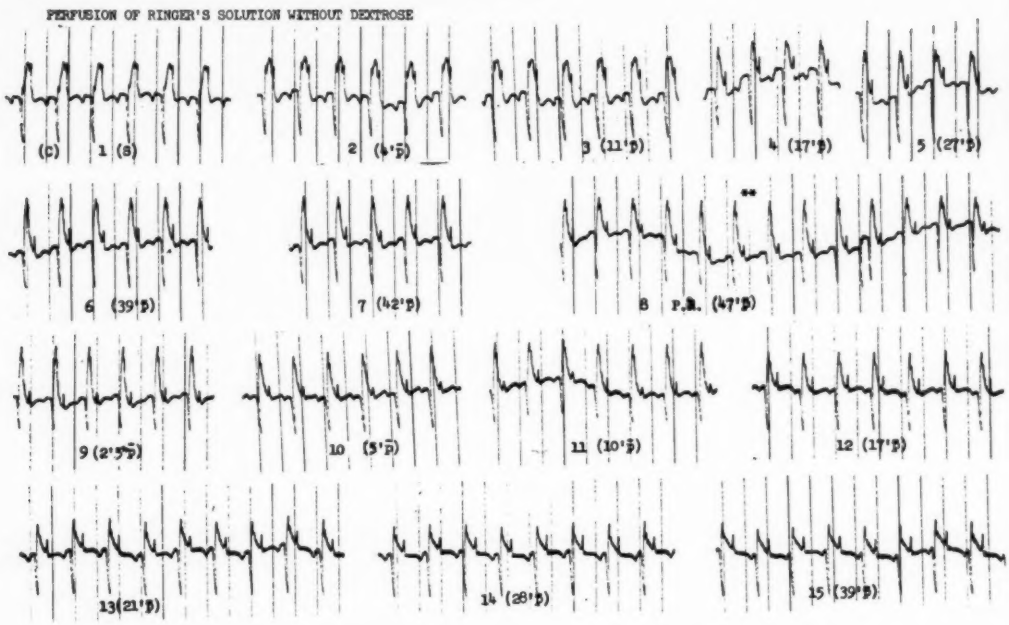

FIG. 2. Electrocardiographic changes following perfusion with oxygenated Ringer's solution without dextrose. Section *1* includes the control tracing (*C*) and start of perfusion with the test fluid (*S*). Sections *2, 3, 4, 5, 6, 7,* and *8* are representative tracings at the times as indicated after perfusion was begun. At ** perfusion with oxygenated Ringer's solution with dextrose was begun, 47 minutes after perfusion with substrate-free fluid had been started. The remainder of the sections are examples at the times indicated. The most apparent change is a decrease in the voltage of atrial and ventricular complexes. There was no atrial or ventricular fibrillation during perfusion with substrate-free solution or in the period of reperfusion with oxygenated Ringer's solution containing substrate.

cur either during perfusion of fluid without dextrose or in the reperfusion period. Electrical arrest did not occur in these hearts perfused with substrate-free solution for periods up to 84 minutes. Although mechanical recovery was poor, the electrocardiogram returned to a control type of pattern in each instance for the period of reperfusion studied up to 83 minutes (Fig. 2).

Perfusion with Ringer's solution with substrate (dextrose) but not oxygenated. In 9 determinations, the average initial amplitude of contraction (control) was 2.8 centimeters, with an average heart rate of 176 beats per minute. Arrest occurred after an average of 69 minutes of perfusion. Immediately upon achieving mechanical arrest, except in 1 case in which there was a 13 minute arrest period, the unoxygenated solution was stopped and perfusion with oxygenated Ringer's solution with substrate was begun. Six hearts did not recover at all. In the remaining 3 hearts, initial recovery occurred after 34, 14, and 11 minutes and maximum recovery at 48, 14, and 48 minutes. The maximum amplitude of contraction after recovery was 31 per cent, 1 per cent, and 7.4 per cent. Heart rate at the time of maximum recovery was 156, fibrillatory, and 132 beats per minute. The hearts were reperfused for periods of 15 to 135 minutes, the average being 53 minutes (Figs. 3 and 4).

Electrocardiograms were done in 6 instances. The changes noted were: (1) decrease in voltage during perfusion with the unoxygenated perfusion fluid; (2) development of irregularities chiefly due to pre-

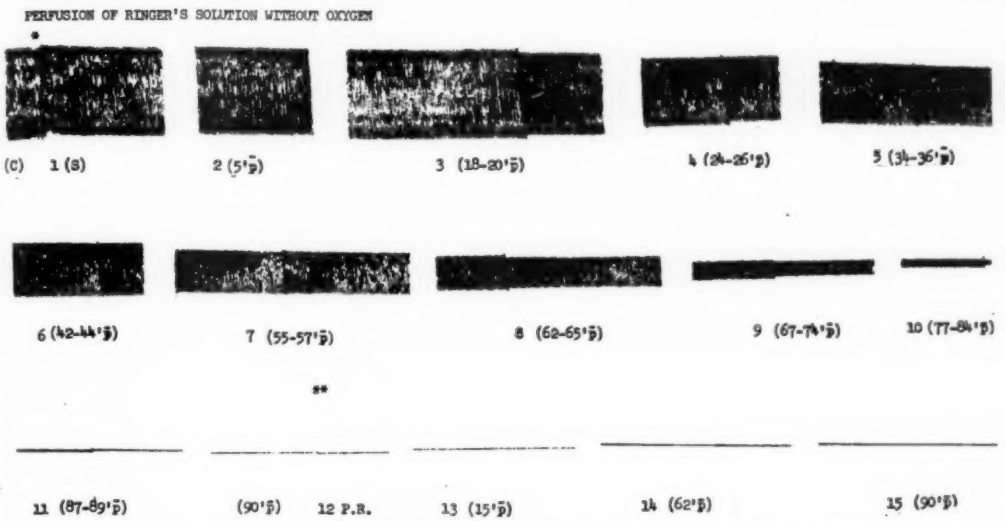

FIG. 3. Recording of amplitude of contraction during perfusion with Ringer's solution containing dextrose but not oxygenated. Control contractile force is indicated by (*C*) in *1*. At (*S*) perfusion with test fluid was started. Sections *2, 3, 4, 5, 6, 7, 8, 9, 10, 11,* and *12* represent contractile forces at the times after perfusion as indicated. At ** perfusion with oxygenated Ringer's solution with dextrose was restarted, 90 minutes after perfusion with unoxygenated fluid was initiated. Sections *13, 14,* and *15* are examples at the times indicated. There was no recovery.

mature ventricular contractions after reperfusion with oxygenated solution; (3) some auriculoventricular dissociation. The electrocardiographic pattern returned to control type except for decreased voltage after 30 minutes of reperfusion. Electrical arrest did not occur in hearts perfused with this unoxygenated solution for periods up to 200 minutes. Although mechanical recovery did not occur in 6 instances and was poor in the remaining 3, the electrocardiogram returned to a control type of pattern, except for decreased voltage, in each case for the period of reperfusion studied up to 135 minutes. There was no atrial or ventricular fibrillation during perfusion of unoxygenated solution or reperfusion with oxygenated Ringer's solution with dextrose (Fig. 5).

Perfusion with Ringer's solution without substrate (dextrose) and not oxygenated. In 8 determinations, the average initial amplitude of contraction (control) was 2.5 centimeters with an average heart rate of 179 beats per minute. Arrest occurred after an average of 49 minutes of perfusion. Immediately upon achieving mechanical arrest, the unoxygenated, substrate-free solution was stopped and perfusion with oxygenated Ringer's solution with substrate was begun. Five hearts did not recover at all. In the remaining 3 hearts, initial recovery occurred after 16, 9, and 8 minutes, and maximum recovery at 42, 22, and 43 minutes. The maximum amplitude of contraction after recovery was 19, 32, and 29 per cent. Heart rate at the time of maximum recovery was 164, 180, and 144 beats per minute. The hearts were reperfused for periods of 10 to 130 minutes, the average being 57 minutes (Figs. 6 and 7).

Electrocardiograms were done in 8 instances. The changes noted were: (1) decrease in voltage; (2) decrease in rate. Electrical arrest did not occur in hearts perfused with this fluid for periods up to 122 minutes. Subsequent perfusion with oxygenated Ringer's solution with dextrose led to some irregularity in rhythm and decrease in amplitude up to 140 minutes after reperfusion. There was no atrial or ventricular

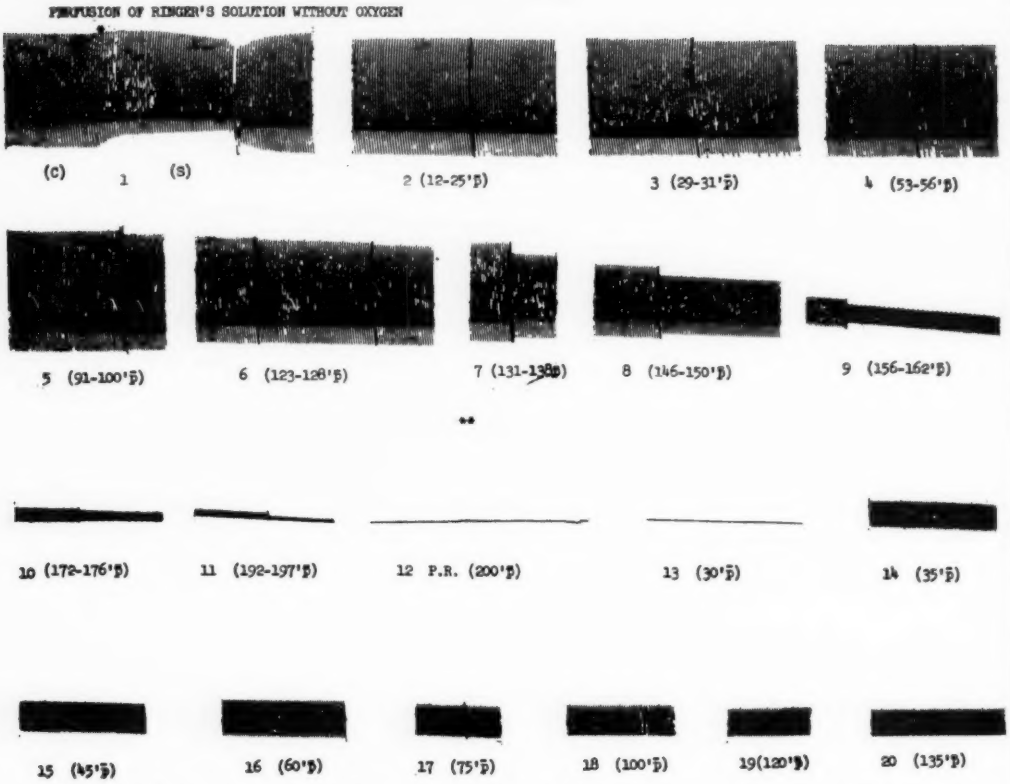

FIG. 4. Similar to the tracings described in Figure 3. Reperfusion was not started until after 200 minutes of perfusion with unoxygenated Ringer's solution. This is one of the hearts that recovered. Maximum recovery, however, was only 31 per cent of the initial amplitude of contraction.

fibrillation during perfusion of unoxygenated Ringer's solution without substrate or reperfusion with oxygenated Ringer's solution with dextrose (Fig. 8).

Cessation of perfusion fluid. In 10 determinations in which the perfusion inflow was clamped off, the average initial amplitude of contraction was 2.0 centimeters with an average heart rate of 192 beats per minute. Arrest occurred an average of 5 minutes and 8 seconds after perfusion had been stopped. The heart arrest was continued for an average of 22 minutes 1 second, after which perfusion with oxygenated Ringer's solution with substrate was begun. Initial recovery occurred after an average of 47 seconds, while maximum recovery was achieved at an average of 5 minutes and 51 seconds. The average maximum amplitude of contraction reached after recovery was 82 per cent of the initial, with a range of 68 to 92 per cent. Heart rate at the time of maximum recovery averaged 205 beats per minute with a range of from 196 to 220 (Fig. 9).

Electrocardiographic determinations done on 4 hearts, arrested for an average of 37 minutes each, revealed that electrical activity persisted long after mechanical activity had ceased. When perfusion was restarted, all hearts showed some degree of fibrillation both atrial and ventricular. In some cases this was marked. On the average, return to a regular rhythm occurred in 4 minutes (Fig. 9).

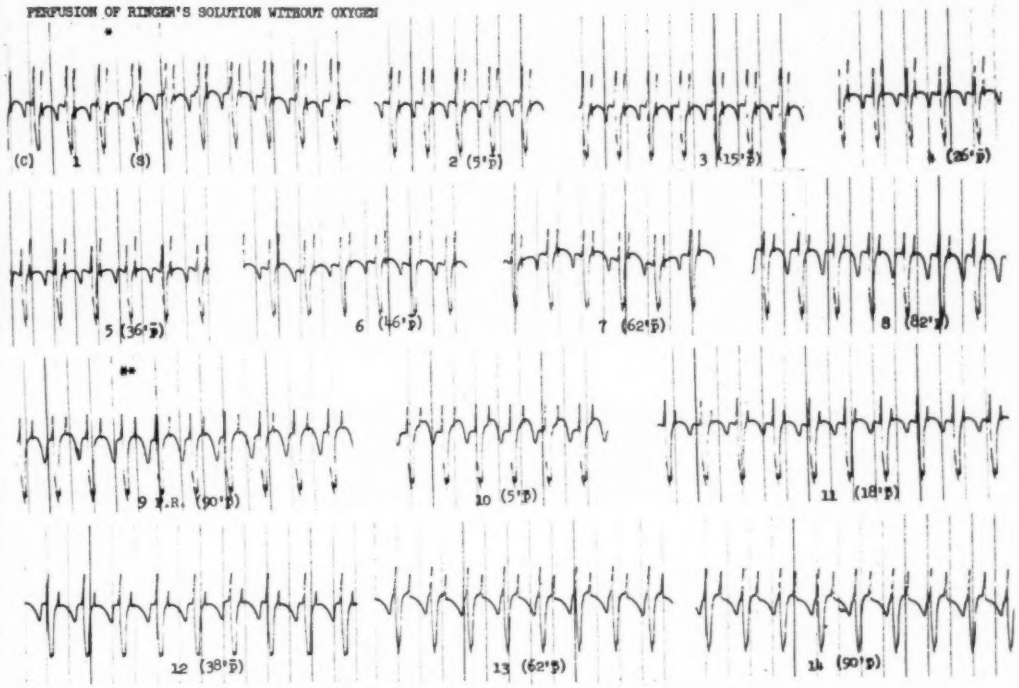

FIG. 5. Electrocardiographic changes following perfusion with Ringer's solution containing substrate but not oxygenated. Section *1* includes the control tracing (*C*) and start of perfusion with the test fluid (*S*). Sections *2*, *3*, *4*, *5*, *6*, *7*, *8*, and *9* are representative tracings at the times as indicated after perfusion was begun. At ** perfusion with Ringer's solution with substrate and oxygen was begun, 90 minutes after perfusion with unoxygenated fluid had been started. The remainder of the sections are examples at the times indicated. The most apparent change in this instance is a decrease in the voltage of the atrial and ventricular complexes. There was no atrial or ventricular fibrillation during perfusion with the unoxygenated solution containing substrate or in the period of reperfusion with oxygenated solution. Despite the fact that mechanical activity did not return in this heart (see Fig. 3), the electrocardiogram 90 minutes after reperfusion, and 90 minutes after arrest of mechanical activity, is like that of the control except for the decreased voltage.

In 4 instances perfusion fluid was clamped off and electrocardiographic recordings were continued for periods up to 115 minutes to determine how long after mechanical arrest, electrical arrest would occur. Mechanical arrest occurred in 2 to 8 minutes after the clamp was applied. Electrocardiographic activity continued for 75 to 115 minutes. The rhythm continued regular throughout the entire period, however, bradycardia developed, evidence of atrial activity disappeared, and voltage of ventricular complexes decreased progressively until electrical activity ceased entirely. When electrical arrest was reached, reperfusion with oxygenated Ringer's solution with dextrose was begun. In each instance, although there was no return of mechanical activity, electrical activity began within 4 to 20 seconds. In most cases, there was an initial return to a control type of electrocardiographic pattern, followed by fibrillation after 2 to 7 minutes. Once begun, the fibrillation continued for the remainder of the experimental period, up to 130 minutes. Stopping the perfusion during this period of fibrillation led to cessation of fibrillation and the development of a regular pattern,

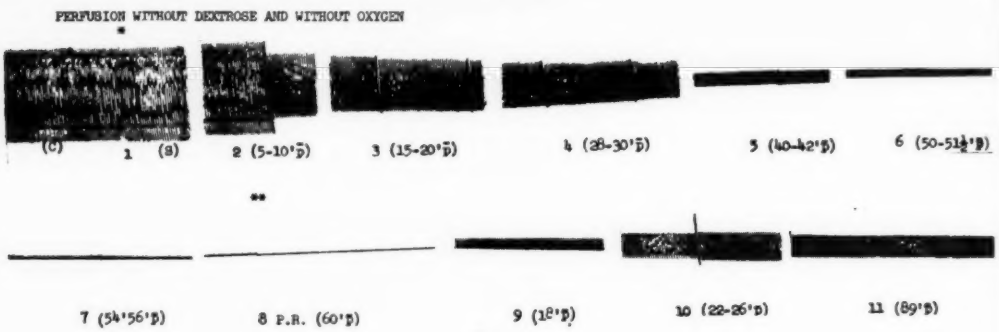

FIG. 6.

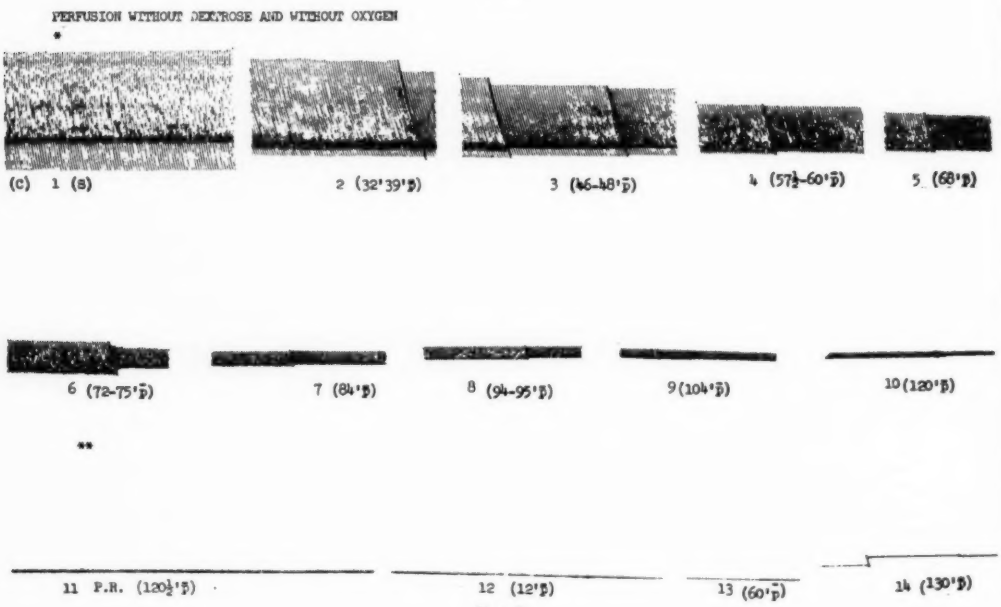

FIG. 7.

FIG. 6. Recording of amplitude of contraction during perfusion with Ringer's solution without dextrose and without oxygen. Control contractile force is indicated by (*C*) in *1*. At (*S*) perfusion with the test fluid was started. Sections *2, 3, 4, 5, 6, 7,* and *8* represent contractile forces at the times after perfusion as indicated. At ** perfusion with oxygenated Ringer's solution with dextrose was restarted, 60 minutes after perfusion with unoxygenated Ringer's solution without dextrose was initiated. Sections *9, 10,* and *11* are examples at the times after reperfusion as indicated. This heart had a maximum mechanical recovery of 32 per cent of the initial amplitude of contraction.

FIG. 7. Similar to tracing described in Figure 6. Reperfusion was not begun until after 120½ minutes of perfusion with unoxygenated Ringer's solution without dextrose. Despite reperfusion with oxygenated Ringer's solution with dextrose for 130 minutes, there was no recovery of mechanical activity.

different from the original and low in amplitude, but regular in rhythm. Removal of the occluding clamp and reperfusion led again to fibrillation (Figs. 10 and 11).

DISCUSSION

Isolated guinea pig hearts perfused with oxygenated Ringer's solution without substrate (dextrose) became mechanically ar-

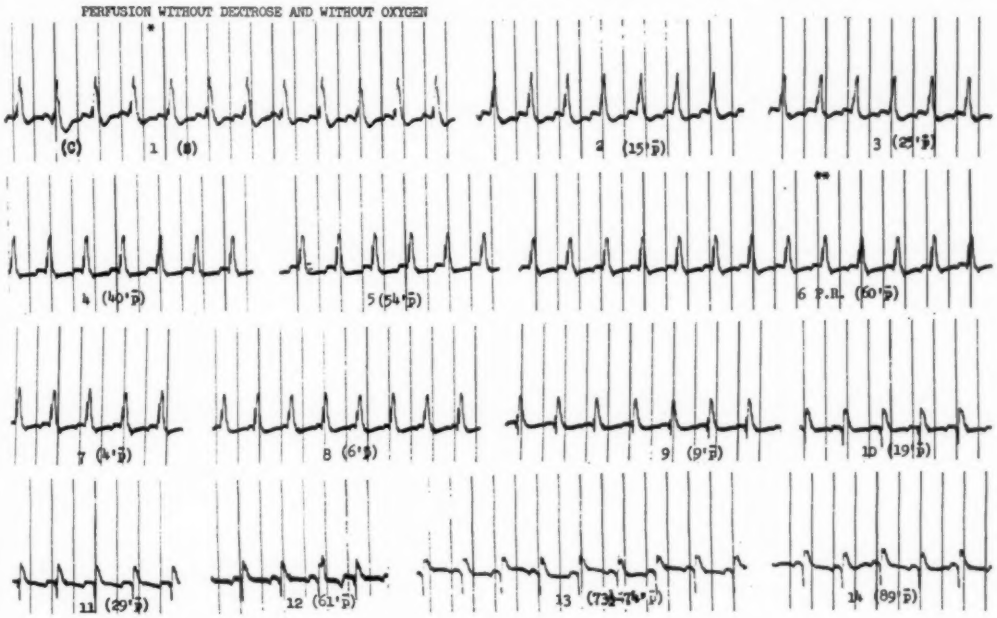

FIG. 8. Electrocardiographic changes following perfusion with unoxygenated Ringer's solution without dextrose. These recordings were taken on the heart with the mechanical record which appears as Figure 6. Section *1* includes the control tracing (*C*) and start of perfusion with the test fluid (*S*). Sections *2*, *3*, *4*, *5*, and *6* are representative tracings at the times as indicated after perfusion was begun. At ** perfusion with oxygenated Ringer's solution with dextrose was begun, 60 minutes after perfusion with the test solution had been started. The remainder of the sections are examples at the times indicated. The most marked changes are decrease in voltage of atrial and ventricular complexes and a decrease in rate. There was no atrial or ventricular fibrillation during perfusion with unoxygenated Ringer's solution without dextrose or in the period of reperfusion with oxygenated solution containing dextrose. The electrocardiographic tracings taken on the heart, the mechanical record of which is indicated in Figure 7, show changes similar to those described. However, despite the fact that mechanical activity did not recur, the electrocardiogram after 150 minutes of reperfusion with oxygenated Ringer's solution with dextrose was present and showed the changes as described for Figure 7.

rested in 47 minutes; those perfused with unoxygenated solution containing substrate became arrested in 69 minutes; while those in which the perfusion fluid was not oxygenated and did not contain substrate were arrested after 49 minutes. Those hearts in which the perfusion inflow was clamped became mechanically arrested in 5 minutes. The fact that in each instance, despite the lack of oxygen or substrate or both, mechanical activity continued for much longer periods than when perfusion was stopped completely indicates that some degree of metabolism was possible when there was oxygen and no substrate, substrate and no oxygen, or even when there was neither oxygen nor substrate. In the first instance, intracellular stores undoubtedly provided substrate materials. Anaerobic or microaerobic metabolic processes may account for the continued activity during perfusion with unoxygenated Ringer's solution containing substrate, or there may have been enough oxygen dissolved in the perfusion fluid to provide minimal metabolic requirements, at least for a short time. The activity that occurred when the perfusion fluid lacked both oxygen and substrate was probably a combination of the factors operating when either oxygen or substrate alone was lack-

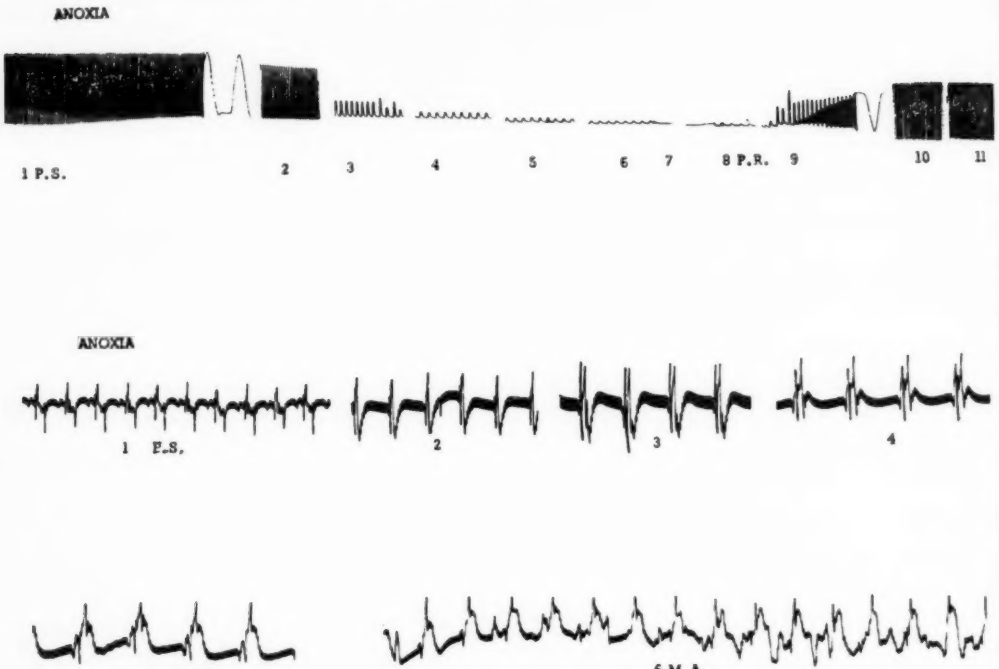

FIG. 9. Tracing of mechanical activity on upper line: *1*, Control amplitude of contraction; *P.S.*, perfusion stopped; *2*, 1 minute; *3*, 3 minutes; *4*, 4 minutes; *5*, 5 minutes; *6*, 6 minutes after perfusion stopped; *7*, mechanical arrest; *8*, *P.R.*, perfusion restarted after 30 minute arrest; *9*, 30 seconds; *10*, 1 minute; *11*, 5 minutes after perfusion restarted with return to maximum amplitude. Electrocardiographic tracings: *1*, control; *P.S.*, perfusion stopped; *2*, mechanical arrest occurred here at 3 minutes 15 seconds after cessation of perfusion; *3*, 9 minutes; *4*, 16 minutes; *5*, 19 minutes after perfusion stopped (15 minutes 45 seconds after mechanical arrest); *6*, *M.A.*, mechanical activity occurred at this point, 20 seconds after reperfusion; *7*, fibrillation about 1 minute 30 seconds after perfusion restarted; *8*, regular pattern following fibrillation; *9*, 5 minutes; *10*, 9 minutes; *11*, 15 minutes after reperfusion.

ing. It is interesting to note that in this latter case, mechanical arrest did not occur as easily as in those hearts in which perfusion fluid was completely stopped. If, as postulated in a previous paper (3), arrest under these conditions is achieved by the accumulation of endogenous potassium, this could not occur under the conditions of the experiment because the continued perfusion would serve to wash out accumulated products of metabolism and cellular breakdown. Thus, with a lack of oxygen and/or substrate, activity of the isolated perfused heart continues for a variable period de-

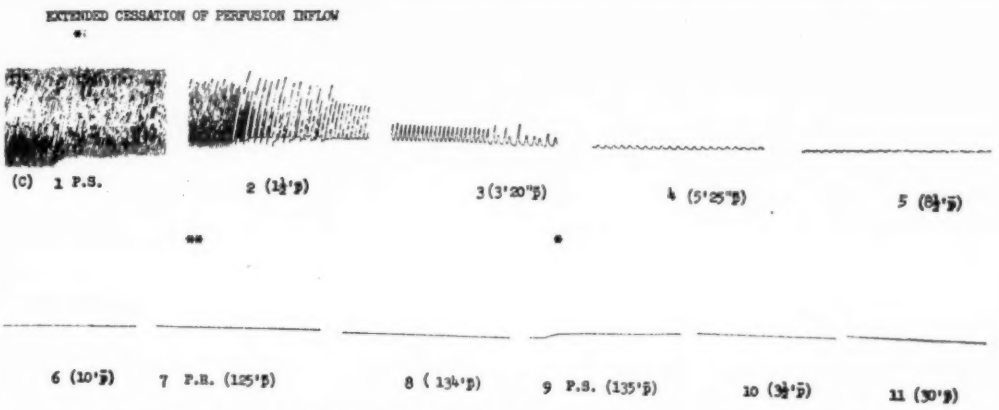

FIG. 10. Recording of amplitude of contraction following cessation of perfusion fluid inflow. Control contractile force is indicated by (*C*) in *1*. At * (*P.S.*) perfusion fluid inflow was stopped. Sections *2*, *3*, *4*, *5*, *6*, and *7* represent contractile forces at the times after cessation of perfusion fluid as indicated. Mechanical arrest occurred about 8½ minutes after perfusion fluid was stopped. At **, in section *7*, reperfusion with oxygenated Ringer's solution with dextrose was begun. There was no recovery up to 134 minutes after reperfusion. At * (*P.S.*) in section *9*, perfusion was stopped again. This caused a rise in base line but no evidence of recovery.

pending probably on accumulated stores of materials that can serve as substrate and on metabolic reactions that can proceed with a minimal amount or, indeed, with no oxygen. Complete cessation of perfusion fluid leads to more rapid consumption of available stores by microaerobic or anaerobic metabolic reactions with probable changes in cellular membrane permeability, accumulation of external potassium, and mechanical arrest.

When reperfusion with oxygenated Ringer's solution containing substrate was begun, all hearts previously perfused with oxygenated solution without dextrose recovered, but only to an average of 56 per cent of their initial values. In those perfused with unoxygenated solution containing dextrose, 6 did not recover and maximum recovery was only 31 per cent. Of those perfused with unoxygenated solution without dextrose, 5 did not recover, and maximum recovery was 32 per cent. These values are much lower than the recovery of contractile force, 82 per cent, in all hearts to which perfusion fluid was stopped completely. It is likely that where there is a lack of substrate, cell stores may be depleted and perhaps cells themselves destroyed. With oxygen lack, incomplete microaerobic or anaerobic metabolic reactions probably come into play. When there is neither substrate nor oxygen, combinations of the previous processes must occur. All of these may lead to a gradual and almost irreversible state of arrest which may be due to cellular exhaustion and derangement of metabolic pathways so that when substrate and oxygen are subsequently delivered, the cells can function only poorly if at all. On the other hand, those hearts arrested by complete cessation of perfusion develop mechanical arrest relatively early. They do not become exhausted and, even after periods of arrest up to 60 minutes, will return to a contractile force about 82 per cent of the initial amplitude when reperfused. Consequently, it would appear more harmful for these hearts to receive either oxygen or substrate alone than to receive no perfusion fluid at all.

Although mechanical arrest was achieved in each instance, electrical arrest did not occur during the test period. The group that had cessation of perfusion and prolonged mechanical arrest did not reach elec-

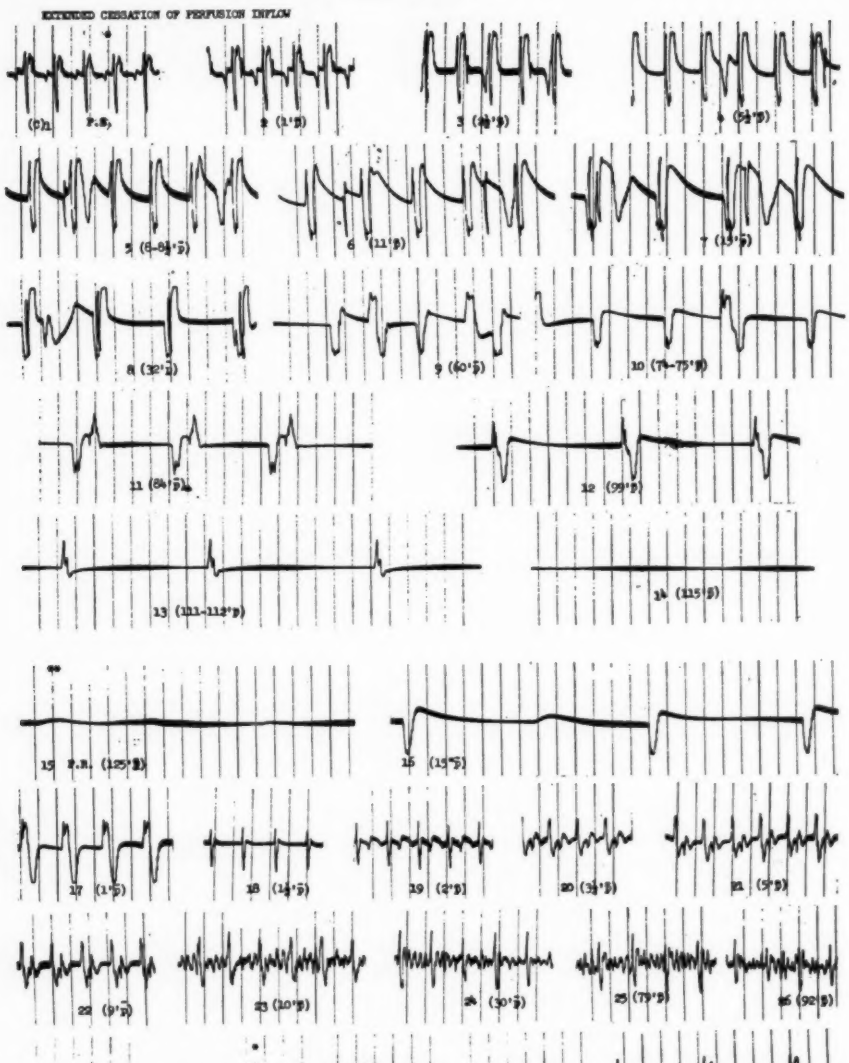

FIG. 11. Electrocardiographic changes after long period of cessation of perfusion fluid inflow (same heart as in Fig. 10). Section *1* includes control tracing (*C*) and cessation of perfusion fluid inflow (*P.S.*). Sections *2* through *13* are tracings at indicated times after cessation of perfusion. Although rhythm continued regular, there was development of bradycardia, loss of atrial activity, and progressive decrease in voltage of ventricular complexes. In section *14*, 115 minutes after perfusion inflow had been stopped, heart became electrically arrested (mechanical arrest had occurred at 8½ minutes). At ** (*P.R.*) of section *15* perfusion with oxygenated Ringer's solution with dextrose was restarted. Initial electrical activity occurred in 15 seconds (section *16*). As seen in *17*, *18*, and *19* there was a return to control type of tracing except for decreased voltage for first 2 minutes after reperfusion. Sections *20* through *27* show development of fibrillation 3½ minutes after reperfusion persisting for 135 minutes. At * (*P.S.*) in section *28* perfusion inflow was stopped. Within 2 minutes fibrillation ceased and a regular rhythm began. Although at outset this resembled the control tracing, the changes already described recurred. A second reperfusion in such cases causes fibrillation which again can be converted to a regular pattern by stopping perfusion.

trical arrest until 75 to 115 minutes after perfusion was stopped. Reperfusion after electrical arrest led to return of electrical activity in seconds. A regular rhythm with low voltage ventricular complexes occurred first, followed by fibrillation that did not revert to a regular rhythm or organized complexes. In all instances the electrocardiographic changes were similar, namely, decrease in voltage, slight bradycardia, and occasional premature ventricular or atrial contractions. Unlike the findings of Penna, who used Tyrode's solution without substrate, there was no atrial or ventricular fibrillation during the perfusion or reperfusion period when oxygenated Ringer's solution without substrate or unoxygenated Ringer's solution with substrate or Ringer's solution with neither oxygen nor substrate was used. However, in the cases in which arrest was achieved by complete cessation of perfusion fluid, atrial and ventricular fibrillation occurred shortly after reperfusion began and persisted for 3 to 4 minutes, after which a regular rhythm was restored.

The fact that mechanical activity returns to a much higher degree and that the electrical response is different when perfusion fluid is stopped completely suggests that a different mechanism leads to the arrest, and the relatively good recovery is based on this fact. The development of the arrest is probably due to accumulation of potassium on the outside of the membrane with subsequent failure of cellular repolarization. When reperfusion begins, accumulated potassium is washed out, and as the high concentration is reduced, fibrillation results until all of the excess is washed out, after which a regular rhythm occurs. The hearts lacking substrate, oxygen, or both in the perfusion fluid, generally undergo an irreversible type of arrest.

It would seem, therefore, that unrecognized periods of hypoxia in a patient undergoing surgery, or under other circumstances during which the coronary arteries are still being perfused with blood containing substrate, could lead to conditions similar to those of the isolated heart perfused with unoxygenated but substrated Ringer's solution. Under these circumstances, cardiac arrest may ensue, and if the duration of hypoxia has been sufficiently long, this may be irreversible. The results indicate that lack of oxygen is more important then lack of substrate in producing irreversible cardiac arrest.

SUMMARY AND CONCLUSIONS

1. The effects of oxygen-free, substrate-free, and oxygen and substrate-free Ringer's solution on the mechanical and electrical activity of the isolated, perfused guinea pig heart have been evaluated and compared with the effects of complete cessation of perfusion fluid inflow.

2. Recovery following perfusion with oxygenated Ringer's solution without dextrose occurred in all instances, but maximum return of amplitude of contraction was only 56 per cent of initial values.

3. After perfusion with unoxygenated Ringer's solution without dextrose, recovery occurred in but 3 of 9 hearts, with maximum return of amplitude of contraction to 31 per cent of initial values.

4. Recovery after perfusion with unoxygenated Ringer's solution without dextrose occurred in 3 of 8 hearts, with maximum return of amplitude of contraction to 32 per cent of initial values.

5. Recovery after complete cessation of perfusion fluid inflow occurred in all hearts arrested for periods up to 60 minutes, with return of amplitude of contraction averaging 82 per cent of initial values.

6. In all instances electrical activity continued long after mechanical arrest had occurred.

7. In hearts subjected to cessation of perfusion fluid inflow for extended periods, electrical arrest occurred 75 to 115 minutes after mechanical activity had ceased.

8. Reperfusion after electrical arrest had been achieved led to rapid electrical recovery which assumed a control type of pat-

tern initially, only to be followed by fibrillation which persisted to the end of the experimental period. Cessation of perfusion fluid inflow converted the fibrillation to a regular rhythm. Reperfusion after this, however, led again to development of fibrillation after an initial period of regularity. Mechanical recovery did not occur in any of the hearts subjected to extended periods of cessation of perfusion fluid inflow.

9. Electrocardiographic changes were similar in all variations tested and consisted of decrease in voltage, slight bradycardia, and occasional premature ventricular or atrial contractions. Following periods of cessation of perfusion fluid inflow, ventricular or atrial fibrillation did not occur except after reperfusion.

10. The difference in mechanical recovery and electrical response in the cases of cessation of perfusion fluid inflow suggests a different mechanism of arrest. This is considered to be based on accumulation of endogenous potassium resulting from changes in cellular permeability. This type of arrest is reversible, while arrest achieved by lack of oxygen, substrate, or both is irreversible and results from cellular exhaustion.

11. The results indicate that lack of oxygen is more important than lack of substrate in producing irreversible cardiac arrest.

12. Possible clinical implications of the results are discussed.

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PERFUSION OF URANIUM-ANTIBODY COMPLEXES FOR THE NEUTRON CAPTURE THERAPY OF TUMORS

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MANY ATTEMPTS have been made to find compounds containing radioactive isotopes which localize in tumors after parenteral injection. The need of maintaining a high ratio of tumor dose to whole body dose during the whole metabolic cycle of such isotopes presents formidable chemical problems.

To circumvent part of the difficulties, nonradioactive materials can be injected which interact with a beam of thermal neutrons from an atomic pile to release alpha particles or fission products toxic to cells. Irradiation can be carried out when distribution ratios are most favorable to maximize effects on tumor while minimizing effects on normal tissue.

Lithium[6] and boron[10], for example, are known to interact readily with thermal neutrons to release alpha particles lethal to cells. At present, boron[10] compounds are being investigated clinically by Sweet and Javid for treatment of brain tumors.

While compounds of boron are desirable because of their low toxicity, energy release following interaction of boron[10] with thermal neutrons is also low in comparison to the fissionable actinides. Interaction of boron[10] with a thermal neutron yields 2.5 million electron volts of energy, most of it given to the resultant alpha particle. Capture of a thermal neutron by uranium[235], by contrast, yields 159 million electron volts of energy distributed among fission products of greater biologic effectiveness than alpha particles. These fission products have a range of action of about 50 microns in tissues, by contrast to the range of about 9 microns for the alpha particle from boron[10] interaction with a thermal neutron.

The main barrier to the use of uranium[235] compounds, for example, has been their toxicity. Since this is seen mainly in the kidney, perfusion of uranium compounds is being investigated in this laboratory to define the contribution that compounds of uranium[235] and other fissionable actinides can make to the neutron capture therapy of tumors.

Several types of uranium compounds are being investigated for perfusion including those containing polar anionic groups for concentration in the periphery of tumors and those containing weak acid groups for concentration in the center of tumors. The group of widest application may be uranium-antibody complexes.

Many attempts have been made to use antibodies against tumors for clinical cancer therapy. If such antibodies can be made to carry one of the fissionable actinides to tumor cells in therapeutic concentration, the power of atomic fission can be linked to the specificity of antigen-antibody interaction for clinical cancer therapy.

For the preliminary investigation of whether uranium complexes of antibodies can be formed which retain antibody specificity, commercially available tetanus antitoxin and tetanus toxoid were used as antibody and antigen. In this article are described attempts to prepare complexes of uranium and tetanus antitoxin suitable for perfusion and to demonstrate retention of antibody specificity of such complexes. If uranium-antibody complexes can be formed which retain antibody specificity, the final step will be to prepare uranium complexes of antibodies against tumor and to use these to

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carry therapeutic doses of uranium to tumor for neutron capture therapy of the tumor.

TECHNIQUES

The femoral artery and vein of dogs were clamped in the groin with bulldog clamps. Polyethylene cannulas were inserted into the vessels below the bulldog clamps and a tourniquet was applied above the clamps. Antigen was injected into the lower calf muscle. Uranium-antibody combinations were then perfused through artery and vein for varying periods of time before release of the tourniquet. Flow rates of about 30 milliliters per minute were used. These could best be obtained by drip into the artery through standard blood administration sets. Gravity drainage of the vein was used. Venous blood, with or without preliminary oxygenation, was periodically added to the arterial intake.

Localization of the uranium was followed by roentgenograms of the dog's leg. Five milligrams or more per milliliter of uranium could be seen, although such roentgenograms reproduce poorly.

MATERIALS

Preparation of uranium-antibody complexes without denaturation of the protein is the main problem. In 1945, McClintock and Friedman published a preliminary report indicating that antibody could be used to localize metals and dyes in tissues. Details of the method used to form the metal or dye-antibody combinations were never published because of the untimely death of Doctor McClintock. It is known, however, that bentonite was used to absorb uranium first, then antibody. Intravenous injection of the bentonite complexes killed guinea pigs in about 20 minutes.

Bentonite complexes of uranium and tetanus antitoxin were first investigated for the present work. No details of the bentonite treatment used by McClintock and Friedman were available, but some fractionation of the bentonite appeared desirable. *United States Pharmacopoeia* and BC micron Wyoming bentonites were used. These were fractionated essentially according to the method of Bloch and Bunim for the preparation of sensitized bentonite particles for serologic test of rheumatoid arthritis activity. Colloidal particles of the size obtained by centrifugation at 500 to 750 times gravity were used. Bloch and Bunim had noted that the specified size range gave sensitized particles whose flocculation could be read at 20 minutes, a time which appeared compatible with that necessary for perfusion of bentonite-antibody complexes.

Despite many variations in the method of combining uranium and antibody to the bentonite, none of the bentonite complexes were found to be suitable for perfusion in the dog. The difficulty was finally traced to the bentonite. While perfusion in control dogs of blood containing high concentration of antibodies without bentonite caused no difficulty, all bentonite complexes or bentonite alone gave rapid gelation of the blood used in the perfusion despite large doses of heparin. In no case in which saline suspensions of bentonite alone or bentonite-antibody complexes had been injected into the femoral artery of the dog could the blood draining from the femoral vein be recycled through the femoral artery because of this rapid gelation. Consequently, bentonite complexes with antibody and uranium were discarded.

Little is known of the exact nature of the chemical bonds holding uranium in its complexes. Consequently, before investigation was to be undertaken of stable uranium complexes linked by covalent bonds to antitoxin, it was decided to investigate loose complexes between antibody and the uranium precipitate formed by addition of alkali and phosphate ion to uranyl acetate in dextran solution.

In a typical run, 800 milligrams of uranyl acetate (reagent grade $UO_2(C_2H_3O_2)_2 \cdot 2H_2O$) were dissolved in 150 milliliters of commercial 6 per cent dextran solution in 0.9 normal saline. With good mechanical stirring, 0.05 normal sodium hydroxide was added over 45 minutes at room temperature

to bring the solution to *p*H 7.5. To the resulting solution was then added 250 milliliters of 0.05 molar phosphate buffer of *p*H 7.3, with good mechanical stirring, over 15 minutes at room temperature. The solution was stirred an additional 15 minutes, then allowed to stand 1 hour at room temperature. The mixture was then centrifuged at 500 times gravity in a refrigerated centrifuge at 2 to 4 degrees C. for 20 minutes. Supernatant was discarded, the sediment made up to 100 milliliters with 0.05 molar phosphate buffer of *p*H 7.3 and the mixture placed in a two speed blender. The mixture was blended for 30 seconds on low speed, then 60 seconds on high speed, then placed in an ice bath for 5 minutes. The mixture was again blended for another 60 seconds at high speed. It was then centrifuged at 750 times gravity for 20 minutes in a refrigerated centrifuge at 2 to 4 degrees C. and the supernatant discarded. The sediment (about 8 ml.) was mixed with an equal volume of 0.05 molar phosphate buffer of *p*H 7.3, then triturated thoroughly in a mortar cooled in an ice bath with 7 milliliters of tetanus antitoxin (2,800 units per ml.). The mixture was allowed to stand 18 to 24 hours at about 5 degrees C. in the refrigerator. It was then centrifuged in 12 milliliter heavy duty centrifuge tubes at 3,300 revolutions per minute for 30 minutes at 2 to 5 degrees C. The supernatant containing excess antitoxin was discarded and the sediment agitated with 8 milliliters of 0.05 molar phosphate buffer per tube, the whole being cooled in an ice bath. The sediment was again recovered by centrifuging at 3,300 revolutions per minute for 30 minutes at 2 to 5 degrees C. The sediment was then made up to 40 milliliters with 0.05 molar phosphate buffer of *p*H 7.3 and the entire mixture thoroughly triturated in a mortar cooled in an ice bath. The mixture was then filtered through a standard blood administration set; the filtrate made up to 50 milliliters with 0.05 molar phosphate buffer of *p*H 7.3 and stored in the refrigerator at 5 degrees C. for use within 24 hours. Before use, an aliquot was counted (beta, gamma, or alpha) and compared with the uranyl acetate used in the preparation for determination of uranium content.

When the perfusion through femoral artery and vein was stable, the appropriate quantity of uranium-antibody complex was diluted with a 3 fold volume of saline and administered into the artery.

For preparation of the antigen used, 30 milliliters of commercial tetanus toxoid precipitated on aluminum phosphate (approximately 12 Lf dose units per ml. and 1 mgm. per ml. of aluminum phosphate) were centrifuged at 5 degrees C. at 2,000 revolutions per minute in 12 milliliter heavy duty tubes for 20 minutes. The sediment was suspended in 3 milliliters of saline and the mixture injected into the lower calf of the dog immediately before perfusion of uranium-antibody complex. The toxoid used assayed approximately 1,235 Lf dose units per milligram of protein nitrogen.

RESULTS

Through use of dilute tetanus toxoid as antigen and 250 milligrams of uranium-antibody complex in the perfusing blood, a faint shadow at the site of antigen injection could be seen on x-ray examination after 15 minutes of perfusion. No such shadow could be seen originally at the site of antigen injection in the lower calf before perfusion. After 1 hour of perfusion, the x-ray shadow sharpened considerably to exceed that cast by 5 milligrams of uranium per milliliter in control dogs injected in the same area of the lower calf.

The blood containing uranium was then washed out of the leg with Ringer's or dextran solution (500 ml.). This fluid never became completely free of red cells. Because of the known ability of citrate to reverse inhibition of enzymes by uranium, 50 milliliters of 4 per cent sodium citrate diluted with an equal volume of saline were then injected into the artery, allowed to drain out through the vein, and discarded.

After "washout" with citrate and suturing of the wound, the x-ray pattern retained the

same general outline but appeared somewhat more granular.

To be certain that the concentration of antibody at antigen site was not a nonspecific adsorption phenomenon of the aluminum phosphate to which the toxoid was adsorbed, 80 milligrams of aluminum phosphate without any toxoid were injected into the lower calf of another control, and the leg was perfused with uranium-antibody combinations. No localization of the uranium-antibody complexes occurred at the site of injection of the pure aluminum phosphate.

DISCUSSION

In the present study, over 5 milligrams per milliliter of uranium could be brought to antigen deposited in the calf by perfusion of uranium-antibody complexes through femoral artery and vein in the groin. The effect was specific. Unless antigen was first deposited in the calf, uranium was not brought there selectively by perfusion of uranium-antibody complexes. Nonspecific adsorbants such as aluminum phosphate do not cause localization of uranium-antibody complexes.

Partial regression in mouse tumors has been seen after intratumor injection of as little as 1 milliliter of a suspension containing 1.5 milligrams per milliliter of $U_3^{235}O_8$ colloid, when the injection was followed by irradiation with thermal neutrons. Therefore, by perfusion, antibodies can be made to bring uranium to antigen selectively at therapeutic dose levels.

The next step will be to prepare antibodies against tumor antigens and to form complexes of these antibodies with uranium^{235} and other fissionable actinides for clinical cancer therapy.

For the work showing therapeutic effects against mouse tumors from intratumor injection of $U_3^{235}O_8$ colloid followed by bombardment with thermal neutrons, an integrated neutron dose of about 10^{12} neutrons per square centimeter was used. This can be obtained within reasonable anesthesia time for patients, inasmuch as neutron fluxes of 10^9 per square centimeter per second and higher are available. With a flux of 10^9 per square centimeter per second treatment time of slightly under 17 minutes would be needed after therapeutic levels of uranium were deposited in the tumor.

Shielding of the rest of the patient presents no problem. As shown previously (2), boron carbide powder can be incorporated into monomer mixes and polymerized in a few minutes at room temperature to yield a custom molded shield which protects all but the tumor from thermal neutrons. If gamma irradiation becomes a problem, lead can also be incorporated into the shielding.

Many problems remain to be solved. Hypercoagulability of perfusing blood was seen along with some vasospasm. As a result, circulation to the leg was restored only partially despite successful suture of artery and vein. The lower leg especially remained cool. The dogs died after 12 to 24 hours. It is believed that this is a technical problem not related to uranium toxicity, since some controls not treated with uranium also died.

Heparin is inadequate as an anticoagulant for this work. In control dogs, when the legs were perfused with Ringer's or Ringer's lactate solution without addition of any uranium complexes, even after 1 hour or more of perfusion, the perfusate from the leg was not free of red cells. On standing, clotting of the red cells in the perfusate occurred. Work is under way on the use of other anticoagulants.

In all of this work, it was found that vasodilators such as procaine reduced the vasospasm. Use of chloropromazine as an antagonist for the possible release of serotonin gave no observable benefits.

The degree of oxygen saturation of the perfusing blood best for treatment of tumors is not yet known. Some decrease in the oxygen saturation of the perfused blood during part of the perfusion may be desirable, with full oxygenation during irradiation. Optimum irradiation times must also be determined.

In the present work, citrate was used as

an antidote to uranium toxicity because of its availability. Other compounds are known to bind uranyl ion more tightly than does citrate and could be added to the arterial side, drained from the venous side, and discarded just as was the citrate in the work described. Complexing agents may also be used to remove daughter products following irradiation so that irradiation to normal tissue would be reduced to a small fraction of that delivered to tumor.

For widespread tumors, it may be possible to inject uranium complexes into the general circulation, while avoiding toxicity to the kidneys by perfusing them with oxygenated blood containing no uranium.

Finally, firmer complexes between uranium and antibody may be needed. It may be best to use covalent bonds to link antitoxin to various complexing moieties which are known to bind uranium tightly.

SUMMARY

Complexes of uranium with antibodies have been prepared for perfusion. The complexes have been shown to be able to carry therapeutic levels of uranium to antigen.

Through use of tumor antibodies linked to uranium^{235} or other fissionable actinides, it should be possible to join the power of atomic fission to the specificity of antigen-antibody interaction for clinical cancer therapy.

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EFFECT OF GASTRIC-DRAINAGE PROCEDURES ON EXPERIMENTAL CANINE ESOPHAGITIS

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REFLUX ESOPHAGITIS has attracted the interest of physicians because its management has been and continues to be a challenging problem. Surgical treatment becomes complicated when the esophagogastric junction is fixed at a supradiaphragmatic level by inflammation and shortening of the esophagus. Under such circumstances, elaborate resective procedures may be required if complicating strictures have occurred. In the absence of this complication, Burford and Lischer suggested that a Finney pyloroplasty, by facilitating gastric emptying, may relieve the symptoms of patients with esophagitis and shortening of the esophagus and lead to regression of the esophagitis. Indeed, some experimental support exists for their findings, and pertinent aspects of this work will be summarized.

Interpretation of the experimental data is difficult, however, because of the diversity of the experimental conditions. In most instances, one or more of the following ancillary procedures have been employed: vagotomy, abdominal positioning of the esophagogastric junction, associated resective procedures, and administration of histamine. Furthermore, in none of the experimental studies were the gastric-drainage procedures carried out after experimental esophagitis already had developed.

The purpose of the present investigation was to study the effect of Heineke-Mikulicz and Finney pyloroplasties on esophagitis induced by a situation closely approximating the clinical condition of a short esophagus hiatal hernia. Neither vagotomy nor resection was done, histamine was not used as a gastric secretory stimulant, and the esophagogastric junction was positioned above the diaphragm.

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METHODS AND MATERIALS

Adult mongrel dogs were anesthetized with pentobarbital sodium given intravenously and were positioned for left anterolateral thoracotomy. During the procedure, respirations were maintained by endotracheal aeration delivered under intermittent positive pressure by means of a mechanical respirator. The pleural cavity was entered through the tenth intercostal space, and the esophageal hiatus was exposed.

In all of the animals, a Heyrovsky-Gröndahl esophagocardioplasty was performed, care being taken to preserve the vagus nerves, and the diaphragm was sutured around the stomach below the anastomosis to create an intrathoracic esophagogastric junction. These animals then were divided into the following four groups for study (Fig. 1): group I (5 dogs) was a control group in which a gastric-drainage procedure was not done; group II (6 dogs) included those in which a concomitant Finney pyloroplasty was performed; group III (5 dogs) comprised those in which a concomitant Heineke-Mikulicz pyloroplasty was performed; group IV (6 dogs) included those in which a Finney pyloroplasty was performed later after esophagitis developed. Gastric secretion was not stimulated postoperatively by the parenteral administration of histamine.

Follow-up studies were made for periods up to 5 months after operation, with period-

ic esophagoscopic examination to evaluate the degree and progression of esophagitis. The degree of esophagitis was graded on the basis of 1 to 3 as follows: grade 1 indicated mild linear esophagitis with reddened granular mucosa; grade 2 denoted a more advanced inflammation with superficial erosion of the mucosa, which bled easily on passage of the esophagoscope; grade 3 indicated frank ulceration of the esophagus.

Necropsy was performed on all the animals.

RESULTS

Group I. As already noted, a Heyrovsky-Gröndahl esophagocardioplasty was done on 5 dogs without a concomitant gastric-drainage procedure. One dog died at reoperation 2½ months after the initial procedure; ulcerative esophagitis was present at necropsy (Fig. 2). Superficial erosions and linear esophagitis were present in 1 animal killed 3 months postoperatively. Linear esophagitis only was present at necropsy 3½ months after operation in another dog. In the other 2 dogs, esophagitis was not present 3 and 3½ months after operation, respectively.

Group II. A Heyrovsky-Gröndahl esophagocardioplasty and a Finney pyloroplasty were performed concomitantly on 6 dogs. One dog died of malnutrition 2 months later; necropsy disclosed grade 3 ulcerative esophagitis (Fig. 3a). Two other dogs died 1 and 2 months later, respectively, with grade 2 esophagitis. The remaining 3 dogs were killed 7 months after operation. At necropsy, 2 had grade 1 linear esophagitis and the other showed no evidence of esophagitis. The latter dog had undergone esophagoscopy at monthly intervals and at no time was any inflammation seen.

Group III. A Heyrovsky-Gröndahl esophagocardioplasty and a Heineke-Mikulicz pyloroplasty were performed concomitantly on 5 dogs. At necropsy 3 and 4 months later, 2 dogs exhibited grade 3 ulcerative esophagitis (Fig. 3b). One dog had grade 1 inflammatory changes at necropsy 7 months later,

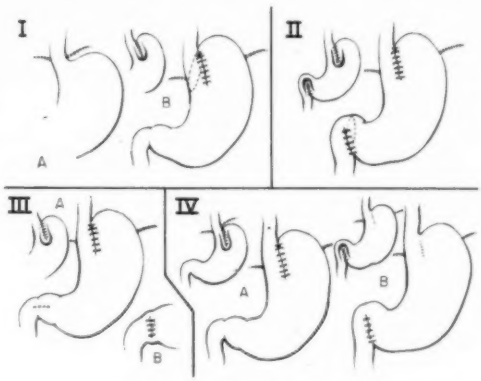


FIG. 1. I*A*, Normal relationship of esophagogastric junction to diaphragm (dotted line). I*B*, Technique of Heyrovsky-Gröndahl operation. II, Combined Heyrovsky-Gröndahl esophagocardioplasty and Finney pyloroplasty. III, Combined Heyrovsky-Gröndahl esophagocardioplasty and Heineke-Mikulicz pyloroplasty. *A*, Pylorotomy incision. *B*, Completed transverse closure of longitudinal incision. IV*A*, Completed Heyrovsky-Gröndahl esophagocardioplasty (first operation). IV*B*, Finney pyloroplasty performed later through an abdominal approach (second operation). In all instances, the widened esophagogastric junction is intentionally placed above the diaphragm after esophagocardioplasty.

whereas the other 2 dogs showed no evidence of inflammation 5 months after operation.

Group IV. A Heyrovsky-Gröndahl-esophagocardioplasty was done on 6 dogs. The animals underwent esophagoscopy at monthly intervals. Depending on the degree and progression of the esophagitis that developed in each dog, a Finney pyloroplasty was performed through an abdominal approach 2 to 5 months after the first operation. Esophagoscopy was done at 6 and 12 week intervals following the second operation. Two dogs had grade 1 esophagitis prior to the Finney pyloroplasty but no evidence of inflammation at necropsy 2 and 4 months later, respectively. Two dogs with grade 2 esophagitis prior to the second operation showed no change at later necropsy (Fig. 4). The other 2 dogs had grade 2 and grade 3 changes, respectively, prior to the Finney pyloroplasty and showed residual grade 1 inflammation at necropsy 5 months after the second operation.

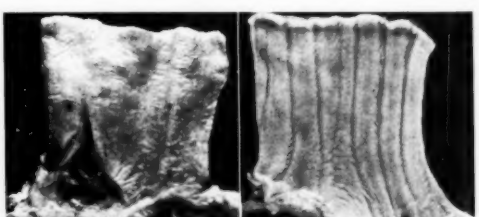
FIG. 2. Esophagogastric junction, showing ulcerative esophagitis 2½ months after Heyrovsky-Gröndahl esophagocardioplasty.

COMMENT

Nyhus and co-workers emphasized the theoretic basis on which a Finney pyloroplasty reduces the secretion of acid from a Heidenhain pouch after vagotomy of the main portion of the stomach in dogs. Stasis of food in the stomach occurs after vagotomy and may lead to prolonged stimulation of the antral mucosa, with an increased output of acid. The rapid gastric emptying produced by a Finney pyloroplasty then will reduce the hormonal phase of gastric secretion, which has been augmented by vagotomy. The mechanism of duodenal inhibition remains unaltered. In comparing the relative effectiveness of different gastric-drainage procedures, Harkins and associates found that three procedures, namely pyloromyotomy, the Heineke-Mikulicz pyloroplasty, and the Finney pyloroplasty, all demonstrated an inhibitory effect on secretion from Heidenhain pouches. Pyloromyotomy, however, was less effective than were the other two procedures in reducing gastric secretion.

Studies done by one of us (Ellis) and associates (3,12) have shown that pyloromyotomy, gastrojejunostomy, or a Heineke-Mikulicz pyloroplasty will not prevent the postoperative development of esophagitis in dogs after esophagogastrectomy when some of the acid-secreting portion of the stomach remains. Kiriluk and Merendino (9,10) have confirmed these findings in esophagogastrectomized dogs with respect to pyloromyotomy and gastrojejunostomy. The results of Girvin and Merendino show that the Finney pyloroplasty reduces the severity of esophagitis, although esophagitis may not be prevented by this drainage procedure. Histamine was administered postoperatively in all these last-mentioned studies, and in none was the Heineke-Mikulicz procedure tested. On the basis of these findings, Merendino and Dillard advocated the Finney pyloroplasty as a protective measure for the transplanted jejunum when this portion of the intestine is interposed between the stomach and esophagus after resection of the cardia in cases of reflux esophagitis and other conditions.

Brackney and associates presented some data on the effectiveness of the Heineke-Mikulicz pyloroplasty in reducing the incidence of esophagitis after surgical destruction of the esophagogastric junction and vagotomy. In other groups of similar studies without this drainage procedure, severe esophagitis was a frequent postoperative finding. When the Heineke-Mikulicz operation was employed as a gastric-drainage proce-



a b

FIG. 3. a, Esophagogastric junction, showing large t i-angular ulceration in a dog which died of malnutrition 2 months after concomitant Heyrovsky-Gröndahl esoph a-gocardioplasty and Finney pyloroplasty. b, Esophagog.s-tric junction, showing superficial ulceration (arrow) 3 months after concomitant Heyrovsky-Gröndahl esoph a-gocardioplasty and Heineke-Mikulicz pyloroplasty.

dure, esophagitis was a rare occurrence. Friesen's (4) experience with the Heineke-Mikulicz procedure is somewhat at variance with these findings; he stated that severe esophagitis developed in dogs after esophagogastrectomy with and without vagotomy despite a concomitant Heineke-Mikulicz pyloroplasty. Similar findings were reported by Friesen and Miller (5) when pyloromyotomy was used as the drainage procedure.

When these experimental studies are summarized, one does not find strong support for the effectiveness of any plastic operation on the pylorus in preventing or reducing the incidence of esophagitis, at least in esophagogastrectomized and vagotomized animals. From the data at hand, the Finney pyloroplasty appears to be more promising in this regard than do the others, but it never has been compared directly with the Heineke-Mikulicz procedure.

Perhaps the most convincing evidence of the effectiveness of the Finney pyloroplasty in preventing the development of esophagitis is that presented by Herron and co-workers. They studied two groups of dogs in which a Heller myotomy was done, the vagus nerves being left intact. A Finney pyloroplasty was done in one group, whereas no drainage procedure was performed in the other. Postoperatively, all animals were stimulated with histamine. The incidence of esophagitis in the controls was 72 per cent, whereas the group that had the Finney pyloroplasty showed an incidence of 9 per cent.

As already noted, the present work was undertaken because so few of the studies even closely mimicked the clinical condition of a short esophagus hiatal hernia and because no clear advantage of the Finney procedure over the Heineke-Mikulicz operation has been presented. The experimental preparation chosen is perhaps not so critical a test of esophagitis-relieving procedures as are others, as stimulation by histamine was not used, yet it does more closely resemble the condition seen clinically. Vagotomy was not done, and the new esophagogastric junction was fixed above the diaphragm.

FIG. 4. Esophagogastric junction, showing superficial erosions in a dog which had a Finney pyloroplasty for grade 2 esophagitis 3 months after a previous Heyrovsky-Gröndahl esophagocardioplasty. Necropsy was performed 5 months after the Finney operation.

As mentioned previously, esophagitis developed in 3 of the control group of animals subjected to a Heyrovsky-Gröndahl operation without a concomitant gastric-drainage procedure. Severe ulceration occurred in only 1 instance. Of the 11 animals in which a concomitant gastric-drainage procedure was done (6 with a Finney pyloroplasty and 5 with a Heineke-Mikulicz pyloroplasty), all but 3 had esophagitis, which was severe in 2. In other words, the incidence of esophagitis in the experimental group was slightly greater than it was in the controls. No clear-cut difference was evident between the results of the two types of pyloroplasties.

When a Finney pyloroplasty was done after esophagitis already had developed, 4 of 6 animals still had evidence of esophagitis at necropsy, although some regression in the severity of the pathologic process was evident in 4. Nevertheless, the over-all results of the present study do not show any striking benefit from pyloroplasty, whether of the Finney or the Heineke-Mikulicz type, as far as preventing the development of esophagitis is concerned or allowing it to heal once it has developed.

It is difficult to know how to apply these

findings to the clinical management of patients suffering from reflux esophagitis. It could well be that the vertical position of man's esophagus as contrasted with its horizontal position in the dog might favorably influence the effectiveness of a gastric-drainage procedure on esophageal reflux. Therefore, rather than conclude from these studies that a pyloroplasty will not be effective, one should await the analysis of clinical results in patients with esophagitis treated by pyloroplasty. However, it would be fair to conclude from these studies that results with either a Heineke-Mikulicz or a Finney pyloroplasty should be comparable.

SUMMARY

The effect of two gastric-drainage procedures, namely the Heineke-Mikulicz and the Finney pyloroplasty, on experimental canine esophagitis has been studied.

The incidence of esophagitis in dogs subjected to Heyrovsky-Gröndahl cardioplasty without concomitant pyloroplasty was slightly less than it was when one or the other of these two gastric-drainage procedures was performed concomitantly.

When a Finney pyloroplasty was done after esophagitis already had developed after a previously performed Heyrovsky-Gröndahl cardioplasty, there was evidence of some regression of the severity of the disease, although most of the animals still showed esophagitis at necropsy.

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SEROTONIN (5-HYDROXYTRYPTAMINE) AND PULMONARY THROMBOEMBOLISM

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SEVERAL recent investigations have been directed toward the hemodynamic aspects of experimental pulmonary embolism. Clots produced by the intravenous injection of topical thrombin have been loosed as emboli as have various inert objects and materials. A role of serotonin (5-hydroxytryptamine) in the physiologic changes observed following pulmonary thromboembolism has been suggested by Comroe and associates and studied by Smith and Smith in cats. However, many variations exist between species, both in sensitivity to serotonin and in the amounts found in the blood and tissues. The present study was undertaken to explore the relationship between the hemodynamics of experimental pulmonary embolism and serotonin in the dog, an animal which resembles man in its responses to serotonin and in the changes in serotonin metabolism produced by drugs. If serotonin were released from a bound to a free active form during pulmonary thromboembolism, the most likely sources of this compound would be the blood and possibly the lung. Therefore, the amount of serotonin present and available is important. By studying both the hemodynamic aspects and the serotonin content of blood and lung in dogs, cats, and humans, it was hoped that a better understanding would be gained of the suggested role of serotonin in the clinical picture of pulmonary thromboembolism.

METHOD AND MATERIALS

Mongrel dogs, weighing 9 to 15 kilograms, were lightly anesthetized with sodium pentothal (20 to 30 mgm./kgm.), and respiration was maintained by intratracheal tube and demand pneophore. A femoral artery was cannulated and catheters placed in the pulmonary artery and left atrium after thoracotomy. Pressures were measured by Statham P-23A transducers and enscribed on a multichannel Sanborn recorder.

Group I (25 dogs). A segment of external jugular vein, 9 to 12 centimeters in length, was isolated between serrefine vascular clamps 1 minute following the intravenous administration of 25 to 90 milliliters of homologous serum. Forty-five minutes were allowed for stabilization before the resulting thrombus was released either intact or as a "shower" of small emboli after serially crushing the vein with a hemostat. In 7 of these dogs, simultaneous femoral and pulmonary arterial blood samples were obtained 15 seconds, 30 seconds, 1 minute, 2 minutes, and 3 minutes following the embolic event and the plasma was analyzed for serotonin spectrophotofluorometrically by the method of Weissbach, Waalkes, and Udenfriend. The animals were sacrificed and the lungs carefully dissected in order to identify and locate the emboli.

Group II (25 dogs). Serotonin was injected intravenously in amounts of from 0.25 to 10.0 micrograms per kilogram. Similar injections were made into the left atrium and ascending and descending aorta for purposes of comparison.

Group III (30 dogs). Mechanical obstruction of one or more lobar arteries was accomplished either by ligature or by the release of 4 millimeter glass beads placed in the external jugular vein.

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TABLE I.—SEROTONIN CONCENTRATION OF WHOLE BLOOD, SERUM, CLOT, AND LUNG

	Whole blood, μgm./ml.		*Serum, μgm./ml.*		*Clot, μgm./ml.*		*Lung, μgm./gm.*	
Species	*Average*	*Range*	*Average*	*Range*	*Average*	*Range*	*Average*	*Range*
Cat	3.4 (10)*	0.90 to 4.5	2.5 (8)	0.30 to 5.7	6.4 (6)	0.60 to 9.60	<0.2† (5)	<0.1 to <0.2
Dog	0.30 (11)	0.20 to 0.80	0.30 (8)	0.20 to 0.60	0.30 (9)	0.10 to 0.60	<0.1 (10)	<0.1 to <0.2
Man	0.10 (10)	0.09 to 0.18	0.11 (6)	0.03 to 0.16	<0.08 (6)	<0.06 to 0.20	<0.2 (5)	<0.1 to <0.3

The concentration of serotonin in the whole blood, serum, clot, and lung of cats, dogs, and humans was determined for comparison between species.
*Parenthesis—total number of animals or patients used.
†Symbol < is used where a distinct fluorescence peak for serotonin was not obtained.

Blood samples were also obtained from normal cats, dogs, and human subjects for determination of serotonin content of whole blood, serum, and clot. The whole blood was allowed to stand 1 to 2 hours before separating the clot and the serum. In addition, the serotonin concentration of human lung, obtained at the time of open thoracotomy, as well as the concentration in the lungs of dogs and cats, was determined. Human blood serotonin was determined by the method of Waalkes; all the tissues, and the blood samples from cats and dogs were analyzed for serotonin by the method of Weissbach and associates.

RESULTS

Satisfactory thrombi were obtained in isolated vein segments following the initial injection of hemologous serum approximately 60 per cent of the time. When firm clotting failed to occur, larger amounts of serum, up to 90 milliliters, were administered from a separate lot of material.

Occlusion of a single lobar artery uniformly caused no pressure changes. Thromboembolization of 2 or 3 lobar arteries usually produced a transient rise in pulmonary arterial pressure of from 2 to 10 millimeters of mercury which gradually returned to normal within 10 to 30 minutes. Systemic and left atrial pressures remained unchanged (Fig. 1). More extensive occlusion, involving more than one main pulmonary artery, resulted in a more pronounced pulmonary hypertension and was accompanied by a transient fall in systemic and mean left atrial pressures. There was no consistent difference between a large single embolus and a shower of smaller emboli obstructing a comparable cross-sectional area of the pulmonary arterial bed.

The pressure changes subsequent to occlusion by glass beads or ligature were virtually identical to those elicited by thromboembolism (Fig. 1).

The intravenous injection of serotonin in amounts of 0.5 to 2.0 micrograms per kilogram resulted in elevations in the systolic pulmonary arterial pressure of 5 to 10 millimeters of mercury, lasting 1 to 4 minutes. This was a reaction comparable in magnitude to that following the occlusion of 2 to 3 lobar arteries. Although obstruction of this magnitude failed to affect the systemic pressure, serotonin injection usually produced a rise of 10 to 50 millimeters of mercury. Occasionally a depressor reaction of lesser degree was observed. A transient 2 to 4 millimeters of mercury elevation of mean left atrial pressure accompanied the rise in systemic pressure (Fig. 1). Larger amounts of serotonin elicited qualitatively similar reactions of increased magnitude, and frequently caused ventricular arrhythmia and bradycardia. Injection of serotonin into the left atrium or ascending aorta usually produced a more marked reaction while a lesser response usually followed injection into the descending aorta.

No significant change in serotonin content could be detected in any of the blood plasma samples obtained during or following the thromboembolic incident. In control studies, however, intravenous administration of at least 10 micrograms per kilogram of serotonin was necessary before a rise in the serotonin concentration was

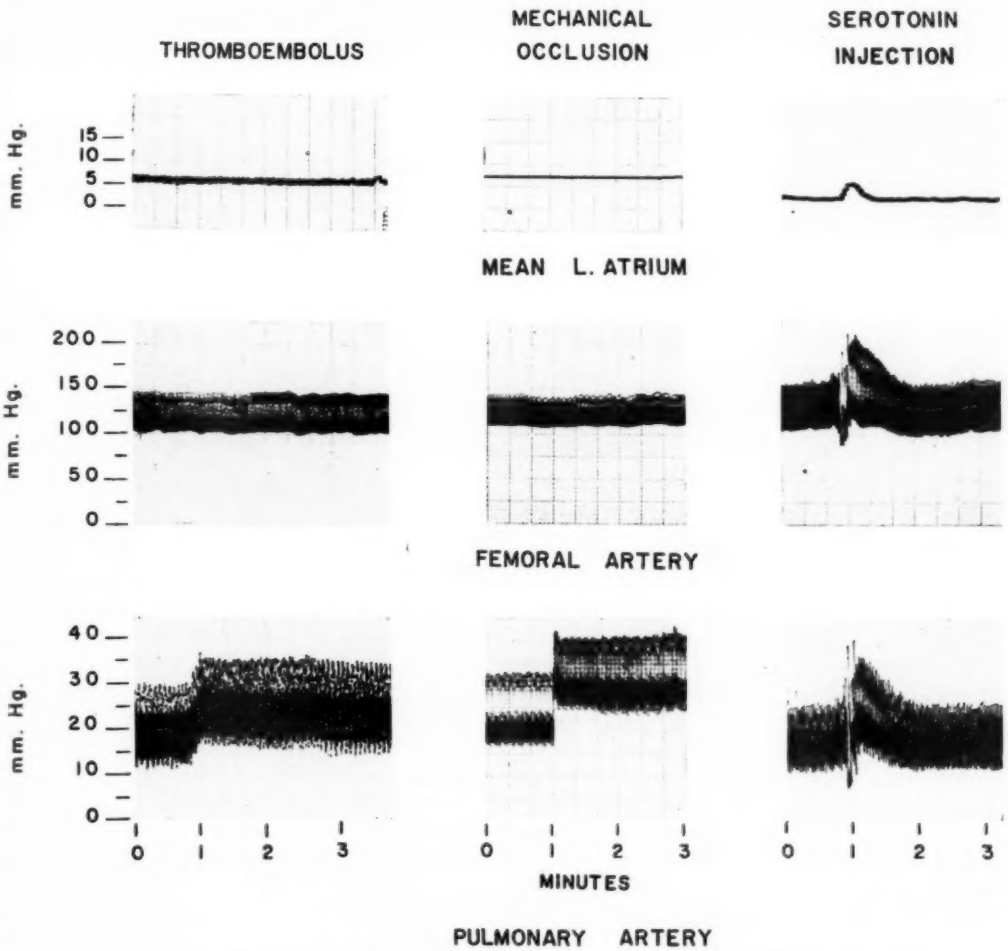

FIG. 1. Comparison of changes in pulmonary arterial, systemic arterial, and left atrial pressures following pulmonary thromboembolism, pulmonary embolism with glass beads, and intravenous injection of 2 micrograms per kilogram of serotonin. While the pulmonary arterial pressure increased in all 3 instances, systemic and left atrial pressures were affected only by the serotonin injection.

found in femoral arterial blood. This dosage provoked a much more pronounced pulmonary hypertension than that seen following embolization.

In Table I the serotonin content of cat, dog, and human blood are compared. The blood of the cat contains more than 10 times the amount of serotonin found in canine blood and more than 30 times that in the human specimens. In addition, there is apparently little if any serotonin in the lung of cats, dogs, or humans.

DISCUSSION

The technique employed in this study for the production of experimental thromboembolism depends upon the induction of a transient state of hypercoagulability by injecting homologous serum containing prothrombin conversion accelerator (SPCA).

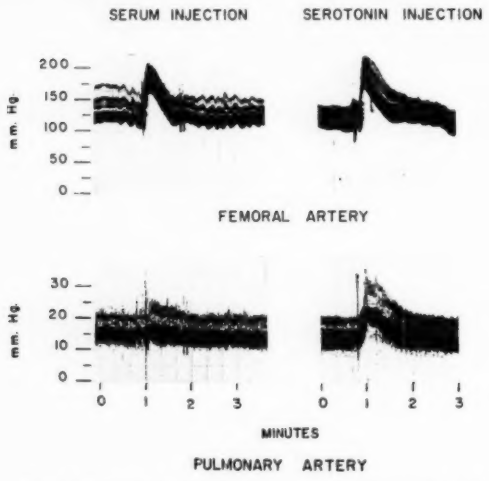

FIG. 2. Comparison of the changes in systemic and pulmonary arterial pressures in a 12 kilogram dog following the intravenous injection of 40 milliliters of homologous serum and, 2 hours later, of 12 micrograms of serotonin.

The method was first described by Wessler, who subsequently extracted SPCA from serum using barium sulfate in order to achieve greater uniformity. This refinement was omitted in the present study because it was thought that repeated injections of homologous serum, in instances when the first injection produced no clots, would be less time-consuming than preparation of the barium extract. Other methods for accomplishing intravascular clotting, such as simple venous stasis, stasis following venous trauma, or the intravenous injection of topical thrombin, were undertaken in preliminary experiments but were found to give less reproducible results.

The pressure changes that followed experimental thromboembolism and serotonin injections were similar in that both produced pulmonary hypertension. However, the significant changes in systemic pressure that usually accompanied the injections of serotonin were not seen following embolization with either thrombi or inert objects. This fact suggests that the hemodynamic sequelae of thromboembolism were not dependent upon a humoral agent, but could be satisfactorily explained by mechanical obstruction. In the pentothal-anesthetized dog, the cross-sectional area of the pulmonary arterial bed which was occluded appeared to determine the nature and magnitude of the response. Occlusion of at least 2 lobar arteries was required before pulmonary hypertension was produced, but a more massive embolic insult was necessary before pulmonary blood flow was sufficiently diminished to be reflected in decreased left atrial and systemic pressures.

Because of its pulmonary vasoconstrictor properties, it was suggested that serotonin might play a significant role in the thromboembolic syndrome. This theory has been explored by Smith and Smith who demonstrated that the embolization of inert objects in cats produced no change in systemic pressure, while pulmonary thromboembolism and serotonin injections were both characterized by systemic hypotension. It has been pointed out by Page, however, that the response to serotonin is highly variable, depending upon the species, anesthetic agent, and vasomotor state of the subject. It has also been observed that the profound hypotensive reaction of the cat to an intravenous injection of serotonin is not typical of the dog or of man. Thus, any conclusions based upon laboratory studies which compare the effects of serotonin with the clinical syndrome of pulmonary thromboembolism must take into account this species variation.

No conclusion can be drawn from the failure to detect an increase in the serotonin level of blood plasma samples obtained subsequent to pulmonary embolization. This was not pursued further when it was found that the intravenous injection of serotonin in amounts (0.5 to 2.0 μgm./kgm.), effecting physiologic changes comparable to the emboli, likewise produced no measurable pressure elevation in the general circulation. Serotonin is carried in the platelets in human blood. However, to our knowledge, the concentration of this amine has never been found to be elevated in the plasma after pulmonary thromboembolism.

The marked species variation in blood content of serotonin is especially noteworthy. The clotting of 1 milliliter of feline blood could release, in the average cat, approximately 3.4 micrograms, enough to elicit the minimal appreciable reaction in a 3 to 4 kilogram cat. In order to release the same amount (1.0 μgm./kgm.) in a 12 kilogram dog, or 70 kilogram man would require the coagulation of 40 milliliters and 700 milliliters of blood, respectively. Figure 2 illustrates that larger amounts of blood serum will indeed elicit responses which are similar to those following serotonin injections.

The relatively large amount of serotonin in cat blood explains why pulmonary thromboembolism in this animal produced pressure changes similar to those following serotonin injection. The much smaller content of serotonin in canine blood explains the absence of this correlation in the present study in the dog. Since the content of this amine in human blood is even smaller than that of the dog, and the content of lung tissue almost negligible, the implication of serotonin as the responsible agent in the clinical syndrome of pulmonary thromboembolism in man becomes more remote.

SUMMARY

Thrombi were produced in the jugular veins of 25 dogs and subsequently released, while pressures were recorded in the pulmonary artery, left atrium, and femoral artery. Pressure tracings were also recorded following the mechanical obstruction of portions of the pulmonary vascular tree and following injections of serotonin. It was found that the pressure changes due to thromboembolism in the anesthetized dog could be explained on the basis of mechanical occlusion and did not resemble the changes elicited by serotonin injections. These results differ from those of other observers who worked with cats. This difference was believed to be due to the much higher concentration of serotonin in cat blood, as compared to dog blood, and perhaps due to species variation in response to serotonin as well. Since the content of this amine in human blood is even smaller than that of the dog, the role of serotonin in the clinical picture of pulmonary thromboembolism in man is probably negligible.

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AN INDWELLING PLASTIC CONDUIT FOR RELIEF OF OBSTRUCTION IN UNRESECTABLE CARCINOMA OF THE STOMACH

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RESECTION with hope of cure is impossible in approximately 50 per cent of patients upon whom laparotomy is to be performed for gastric carcinoma. Of the remainder, palliative resection is feasible in approximately one-third, and in a much smaller number enough uninvolved stomach may exist above the obstructing neoplasm to warrant a palliative gastroenterostomy. In the unfortunate remainder, which comprises almost one-third of all patients who submit to laparotomy, diffuse tumor involves the entire stomach, and palliative resection or bypass is not possible. These patients are committed to relentless obstruction and starvation. This study represents an evaluation of the palliation obtained by the use of an indwelling large bore plastic conduit which has been passed through the obstructing gastric carcinomas at the time of laparotomy in 15 patients when no other relief from obstruction was possible.

CLINICAL EXPERIENCE

In 15 patients with carcinoma of the stomach so extensive that neither resection nor operative bypass was feasible, varying lengths of molded plastic tubes have been passed through the tumor to relieve obstruction. A short discussion of each case follows.

CASE REPORTS

CASE 1. H. S. J. (Fig. 1), a 66 year old man, at laparotomy on September 27, 1956, had a large fungating completely obstructing, annular carcinoma of the antrum with generalized peritoneal carcinomatosis. Palliative resection was impossible because of posterior fixation of the tumor. A soft polyethylene Berman tube was passed, via a high gastrotomy, through the obstructing lesion and fixed to the stomach wall with interrupted heavy silk sutures.

By the fifth postoperative day he was on a full liquid diet. He was discharged on October 15, 1956 on a low residue diet. He ate well, began to gain weight, but 6 weeks later (2½ months following operation) was readmitted in a moribund condition. Autopsy on December 10, 1956 revealed partial obstruction of the distal end of the straight Berman tube due to failure of this type of tube to conform to the curvature of the duodenum.

CASE 2. W. McC., a 65 year old rancher, had complete pyloric obstruction prior to laparotomy on July 3, 1957, at which time an extensive linitis plastica was found to involve the entire stomach. Through a duodenotomy a mayon plastic tube was inserted through the tumor with its proximal end in the fundus and its distal end in the duodenum. Fixation of the tube was attained by mattress sutures of heavy silk through the duodenum and the wall of the plastic tube. By the third postoperative day the patient tolerated a full liquid diet. By the time of his discharge, 12 days postoperatively, he was eating a soft diet. He returned home and spent the remaining 7 weeks of his life in relative comfort, fishing and visiting old friends. On September 4, 1957 he suddenly went into a coma and died 2 days later from a cerebral metastasis, having had effective palliation for 2 months.

CASE 3. A. W. R., a 63 year old timberman, was unable even to retain clear liquids. At laparotomy on August 2, 1957 an extensive carcinoma was found to involve the entire lesser curvature and fundus of the stomach as well as the lower esophagus. There were extensive liver metastases. A contoured mayon tube was forced through the obstructing tumor by using the Levin tube as a guide. By the end of the first postoperative week he was taking a soft diet and was discharged 3 weeks postoperatively. He continued to be able to eat without undue discomfort within a few

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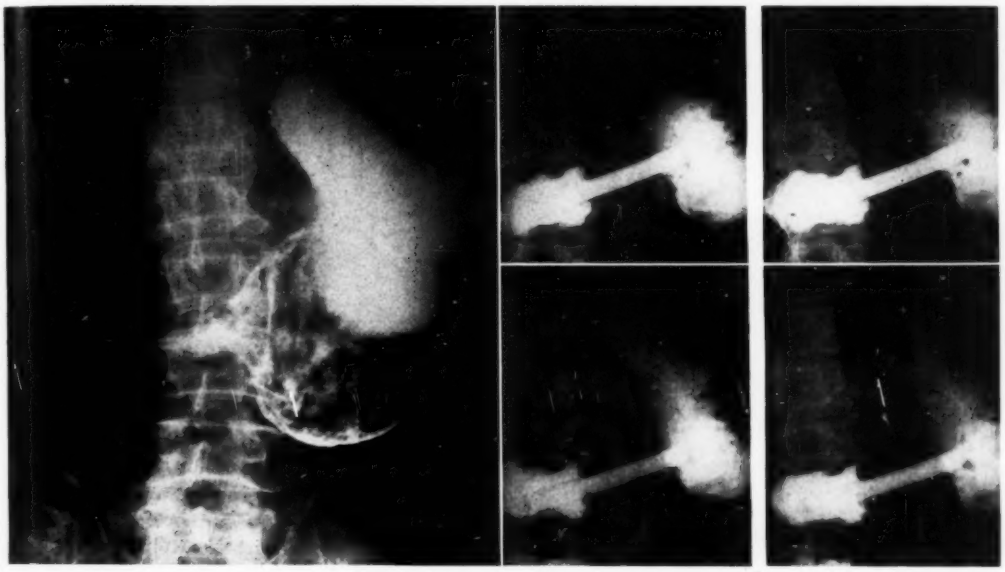

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FIG. 1. Case 1. a, Preoperative roentgenogram, showing obstruction due to antral carcinoma. b, Postoperative, showing barium passing through the conduit at the pylorus.

days prior to his death on September 27, 1957, despite the fact that the proximal end of the tube edged slightly below the border of the tumor. This patient had palliation from the obstruction for almost 2 months.

CASE 4. E. M. C. (Fig. 2), a 34 year old bricklayer, was found on August 27, 1957 to have an extensive carcinoma of the entire stomach with liver metastases. Although the obstruction was not complete at the time of exploration, a contoured mayon conduit was forced through the tumor and tailored to extend from the lower esophagus into the second portion of the duodenum. By the third postoperative day, he began eating a soft diet which he tolerated without difficulty until his death from an exsanguinating gastric hemorrhage on January 25, 1958. During the 5 months following insertion of the tube he occasionally had mild back pain and belching which might have been due to the tube in the lower esophagus. At autopsy the terminal hemorrhage was found not to be related to gastric erosion around the plastic tube.

CASE 5. C. T. C., a 63 year old man, at laparotomy on September 10, 1957, had a huge obstructing carcinoma involving the entire body of the stomach and the pancreas with extensive intraperitoneal implants. A molded mayon tube extending from the lower esophagus to the second portion of the duodenum was inserted through a duodenotomy. By the time of discharge from the hospital on the nineteenth postoperative day he was taking a soft diet without evidence of obstruction or dysphagia. He ate well until the day of his sudden death at home on October 29, 1957.

CASE 6. M. W., a 50 year old man, on August 20, 1955, had a partial gastrectomy and esophagogastrotomy for carcinoma of the stomach. He had adequate palliation postoperatively but gradually obstruction became complete at the site of the anastomosis. On September 17, 1957 a molded mayon tube was forced through the recurrent tumor via a gastrotomy incision. Postoperatively he was able to take a soft diet and left the hospital 23 days thereafter. He tolerated his low residue diet well, but on November 16, 1957 a bolus of food suddenly obstructed the tube which had to be removed by laparotomy. Thereafter obstruction became complete and he died on December 11, 1957.

CASE 7. G. H. R., a 63 year old man with recurrent gastric carcinoma, underwent re-exploration on October 28, 1957 because of obstruction following a palliative Billroth I subtotal gastrectomy performed 6 months previously. Although there was an uninvolved portion of the stomach proximal to the tumor the surgeon chose to thread a molded mayon tube through the tumor, which was anchored with but 1 stitch into the stomach wall. Postoperatively the obstruction remained complete and the tube was found on x-ray examination to have passed into the large bowel. Another laparotomy was performed on November 6, 1957 when the tube was pushed through the rectum and a bypassing gastroenterostomy was also per-

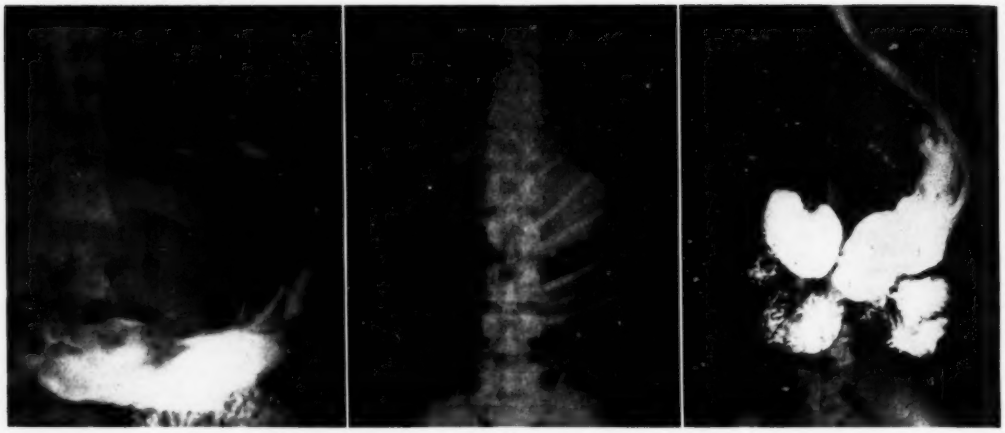

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FIG. 2. Case 4. a, Preoperative roentgenogram, showing linitis plastica extending from gastroesophageal junction to antrum. b, Postoperative, showing plastic tube in place. c, Postoperative, showing barium passing through plastic tube from esophagus into distal portion of stomach and duodenum beyond the obstructing tumor.

formed—a procedure that in retrospect was indicated rather than insertion of the plastic tube. Obstruction was relieved but the patient died November 25, 1957.

CASE 8. I. M. (Fig. 3), a 40 year old man, had complete obstruction from recurrent carcinoma of the stomach at the site of his previous esophagogastrotomy. On November 11, 1957 a molded mayon tube extending from the lower esophagus to the duodenum was passed through the obstructing lesion and fixed to the stomach and duodenal wall in the usual manner. Postoperatively he noted some belching and vague substernal and back pain but was markedly satisfied with the procedure and was able to eat a soft diet up until the day before his death from widespread pulmonary metastases on December 24, 1957.

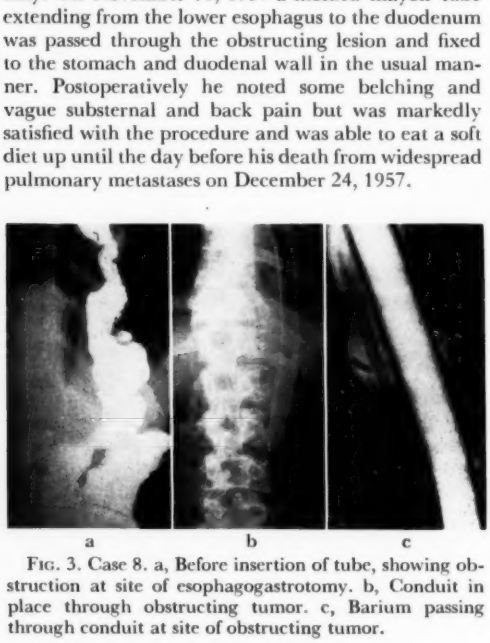

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FIG. 3. Case 8. a, Before insertion of tube, showing obstruction at site of esophagogastrotomy. b, Conduit in place through obstructing tumor. c, Barium passing through conduit at site of obstructing tumor.

CASE 9. D. O. D., a 54 year old man, had complete obstruction at the time of laparotomy on November 21, 1957. A bulky carcinoma of the fundus and body of the stomach was found which invaded the celiac artery and aorta. The proximal end of a molded plastic conduit was forced into the midesophagus through the obstructing tumor with the distal end of the tube lying at the pylorus. By the third postoperative day he was taking a mechanically soft diet and was discharged 10 days following insertion of the tube. He gained strength and weight and resumed his part time employment as a construction worker. When seen on March 25, 1958 he had gained some weight. He complained of occasional hiccough and some regurgitation if he remained prone immediately after eating but slept comfortably propped on 2 pillows and his mild symptoms of pyrosis were relieved with an antacid. He received cobalt radiation with x-ray evidence of shrinkage of the tumor. Seven months and 5 days after insertion of the tube he died suddenly, and autopsy revealed perforation of the esophagus and aorta by the proximal end of the tube.

CASE 10. A. C., a 78 year old man, with almost complete obstruction was found at laparotomy on February 18, 1958 to have a large obstructing adenocarcinoma of the cardia of the stomach with massive periaortic metastases. A molded mayon conduit was thrust into the esophagus through the tumor, and the distal end of the tube was anchored in the prepyloric area of the stomach. By the fourth postoperative day he was taking a soft diet and continued to be able to maintain his weight during the radiation therapy started soon thereafter. He had comfortable palliation until his death 5 months later.

CASE 11. H. C. G., a 63 year old man, with pernicious anemia of 16 years' duration had almost complete obstruction from a carcinoma of the stomach. Exploratory laparotomy on April 18, 1958, revealed obstruction and multiple regional metastases. A mayon tube was inserted through a duodenotomy incision. The postoperative course was smooth and he was able to take a soft diet by his fifth postoperative day and soon returned home. Gastrointestinal bleeding developed which became quite extensive. He expired on May 11, 1958, 23 days after insertion of the tube. Autopsy revealed that the tube was functioning well and that the patient had bled from the large tumor of the stomach.

CASE 12. O. W. R., a 45 year old man, suffered a 70 pound weight loss due to an obstructing adenocarcinoma of the esophagogastric junction, which extended into the lower one-third of the esophagus. At exploration on June 18, 1958, multiple metastases were found. A 20 centimeter long mayon tube was pulled through the obstructing tumor by use of a Levin tube and a pull-out suture. Six days thereafter a wound dehiscence required closure but 5 days later he was able to take a mechanical soft diet. He was discharged and traveled to California, where his physician reported he was able to eat but had a slowly downhill course and expired on September 1, 1958.

CASE 13. L. B., a 66 year old man, lost 35 pounds of weight during the 3 months prior to admission because of a progressively obstructing adenocarcinoma of the esophagogastric junction. At operation on July 3, 1958 the lesion was found to extend 14 centimeters up the esophagus with almost complete obstruction at the cardia, and to be accompanied by extensive peritoneal implants. A mayon plastic tube was pulled through the lesion from an incision in the stomach. Postoperatively the patient took a liquid diet on his third day and was discharged on the seventh postoperative day taking a soft diet and doing well. He maintained his weight on a soft diet for 6 months and only began to lose weight and strength 1 month ago. At the present time (February 1959) he appears terminal but there is no obstruction.

CASE 14. This 58 year old man had had an anterior gastrojejunostomy performed elsewhere for an extensive unresectable gastric carcinoma. Obstruction at the anastomotic site was complete and on August 5, 1958, 1 month following his original operation, an exploratory operation was again performed and a short (10 cm.) length of mayon tube was forced through the obstructed anastomotic site. Postoperatively he did poorly, a gastrocutaneous fistula developed, and he died 20 days following insertion of the prosthesis. Postmortem demonstrated that a rapidly growing tumor had grown into and obstructed the tube.

CASE 15. J. S., a 66 year old farmer, had almost total obstruction 3 months following resection of the distal one-third of the esophagus and subtotal gastrectomy for an adenocarcinoma of the gastroesophageal junction. He lost 42 pounds and was barely able to drink clear liquids. At re-exploration on August 25, 1959, the tumor was found obstructing the esophagogastric junction. A mayon tube was passed through the obstructing tumor and anchored with 3 silk sutures. Postoperatively he was able to take a soft diet and went home on the seventeenth postoperative day. Palliation was excellent for 4 months, at which time hemiplegia developed from brain metastasis, and at the present time (February 1959), 5½ months after insertion of the plastic conduit, he is reported to be in a near terminal condition.

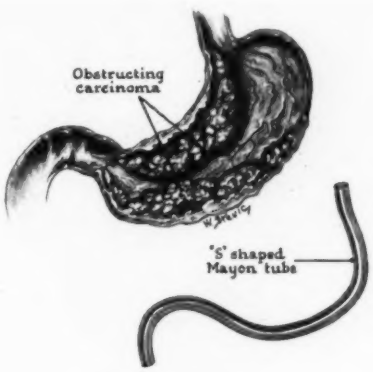

FIG. 4. The type of unresectable gastric carcinoma in which the conduit is employed.

DISCUSSION

Plastic tubes have previously been employed in the palliative management of obstructing carcinoma of the esophagus, and the use of such semirigid conduits in the stomach is merely an extension of this concept. In 1952 Berman used polyethylene tubes to bridge the hiatus left after palliative resection of obstructing esophageal carcinoma. Others have reported passing such tubes through the obstructing esopha-

FIG. 5. The fenestrated end of the tube fashioned at the time of operation.

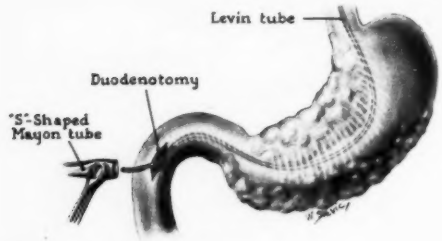

FIG. 6.

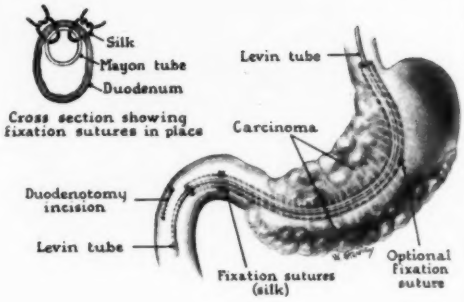

FIG. 7.

FIG. 6. Conduit about to be slipped over a Levin tube guide through a duodenotomy.
FIG. 7. Conduit in place showing anchoring heavy silk sutures passed through duodenal wall and side of plastic tube.

geal tumors at the time of operation without attempting resection. The endoscopic placement of such indwelling conduits within the esophagus has also been reported.

When at laparotomy gastric carcinoma extends beyond the confines of surgical cure most surgeons advocate a palliative resection if obstruction is imminent and sufficient uninvolved stomach exists proximal to the tumor. The advisability of anastomotic bypass procedures under these circumstances is more debatable. It is in these unresectable obstructing gastric cancers that palliation from obstruction by the use of an indwelling plastic conduit is worthy of trial.

After considerable experiment, tubes made of mayon were judged to have the requirements most suited to this purpose. Such tubes produce minimal reaction within the intestinal tract, are firm enough to hold shape despite the pressure of an encircling tumor, yet at body temperature are sufficiently pliable to avoid serious erosion of the adjacent intestinal wall. Molding of the plastic to conform to the silhouette of the involved intestinal tract also reduces the likelihood of such erosion. Tubes of this material are easily and cheaply constructed by slipping 40 centimeter lengths of the tubing over a metal mold fashioned in the contour of the lower esophagus, stomach, and duodenum. By autoclaving the tube fashioned in this manner at 240 degrees F. for 10 to 15 minutes, the plastic retains the shape of the mold after it is allowed to cool. The tubes thus contoured in the shape of the upper intestinal tract are cold sterilized by immersion in alcohol or other bactericidal agent and sterilely wrapped until required at operation.

Two sizes of such tubes have been utilized: the smaller, 5/8 inch (15.8 mm.) outside diameter with a lumen of 12.7 millimeters, the larger size tube with a 7/8 inch (22.2 mm.) outside diameter and a lumen of 5/8 inch (15.8 mm.).

When at laparotomy the surgeon finds the obstructing lesion to be unresectable the extent of the tumor is determined and a length of the plastic tube cut along its appropriate contour so that 4 to 6 centimeters of the tube extend both above and below the gross confines of the tumor (Fig. 4). The proximal and distal cuffs of the tube which are destined to extend beyond the tumor are then fenestrated by cutting 3 concentrically placed windows in the tube, using wire-cutting or other heavy scissors (Fig. 5). These openings prevent obstruction of the end of the tube by a single bolus of food as occurred in Case 6.

The tubes are inserted through a short duodenotomy or gastrotomy incision made immediately distal to the tumor, as illustrated in Figures 6 and 7. In some cases the wide plastic tube can be manually forced

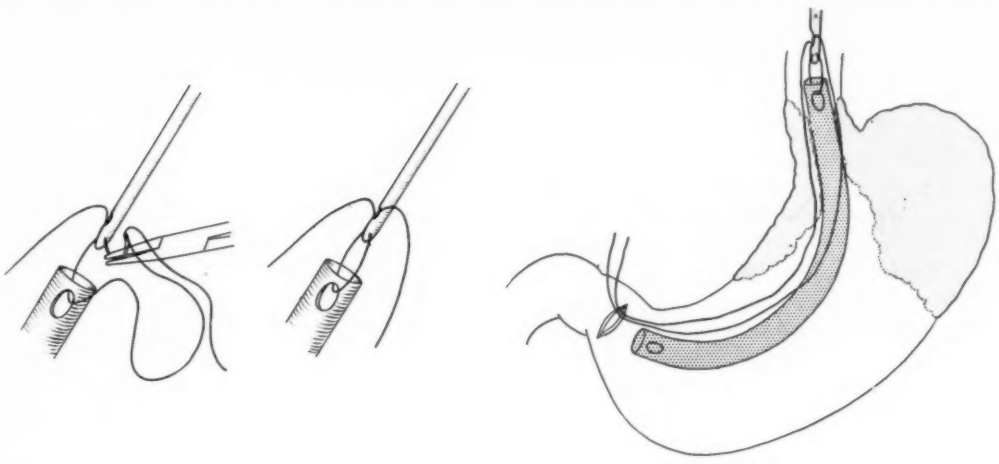

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FIG. 8. a, Placement of pull-out suture through Levin tube used in drawing conduit through an obstructing tumor. b, Conduit in place with pull-out sutures ready to be removed through duodenotomy.

through the tumor so that its proximal end lies well above the lesion in uninvolved stomach or esophagus. In other cases blind forcing of such a passage may be either impossible or inadvisable for fear of perforating the involved stomach wall. In such instances the conduit must be pulled proximally through the obstructing tumor by a Levin tube which preoperatively has been passed from the nose through the tumor. By temporarily fixing the plastic conduit to the Levin tube with a pull-out suture, as shown in Figure 8, the tube can be drawn proximally through the obstrucing tumor, following which the Levin tube can be freed from the conduit. Thereafter the Levin tube can either be withdrawn or passed through the lumen of the conduit for temporary postoperative suction. If a Levin tube cannot be passed from above through the obstructing tumor a similar guide can be made by utilizing a swallowed string with a bowline loop placed in its distal end.

Fixation of the tubes is achieved simply by placing 3 or more heavy (No. 2 silk) mattress sutures circumferentially through the wall of the tube and the adjacent wall of the stomach or duodenum. More secure anchorage can be attained by using a wide mattress stitch in the duodenal wall in order to avoid the suture working its way out, as occurred in Case 7. Normally it is not possible to anchor the tube proximally, for the stomach is extensively involved in tumor, but in such instances the tumor itself maintains placement of the plastic conduit. If even a small portion of the proximal stomach is uninvolved with tumor an accessory anchoring stitch is indicated.

The anchoring stitches must not traverse the lumen of the plastic tube lest they form a web upon which food particles may impinge and produce obstruction.

After proper placement and fixation of the conduit, the duodenotomy is closed. The entire preparation and fixation of the tube takes but a few minutes and adds little to the stress of simple exploratory laparotomy.

Evaluation of the results so far attained by the use of these tubes suggests that they offer worthwhile palliation to the patient when other surgical means cannot relieve obstruction due to a gastric carcinoma. Prior to operation each of these 15 patients had varying obstructive symptoms, ranging from occasional vomiting to inability even

to retain clear liquids. Following insertion of the plastic conduit all have been able to tolerate a full liquid or soft solid diet during the months of life remaining.

Discomfort due to the tubes has been minimal, albeit difficult to evaluate because of the underlying neoplasm. In no patient could increase in abdominal discomfort be ascribed to the tube. There was no operative mortality in this small series. In 3 of the 5 patients in whom the tubes were threaded into the esophagus there were mild symptoms of esophagitis when the patient lay prone. In 1 case this was relieved by an antacid (despite achlorhydria), and in another by sleeping propped on 2 or 3 pillows. In no case was such discomfort crippling. When the tubes did not extend above the fundus of the stomach they produced no such symptoms. The 2 cases in which there was serious morbidity ascribable to the tubes should be judged as technical errors. In 1 individual (Case 7) improper fixation allowed the tube to come loose and pass down the intestinal tract. In another, the tube had to be removed when a large piece of meat caught on an improperly placed suture that traversed the lumen of the plastic conduit. Such technical errors occurring in our early experience have prompted alterations in technique so as to avoid their repetition.

Exploratory laparotomy was performed on 7 patients known to have tumor recurrence following previous gastric surgery. In 5 cases (Cases 6, 7, 8, 14, and 15) palliation resulted from insertion of the tube. In 2 others it was impossible to introduce the tube into the intestinal tract because of extensive tumor recurrence overlying the stomach and duodenum. This experience raises the question as to the advisability of trying to insert such plastic tubes in a patient with a known recurrence following a previous gastrectomy. Their insertion through a postoperative site further confused by local tumor recurrence is obviously difficult. Since these tubes are of proved value in the occasional case of this type, the surgeon must try to select the patient with proved recurrence who will withstand the procedure, has a reasonable expectancy if obstruction is relieved, and in whose case abdominal palpation suggests that the first portion of the duodenum can be exposed without undue difficulty.

SUMMARY

1. Segments of a plastic tube molded in the shape of the lower esophagus, stomach, and duodenum have been placed as a permanent indwelling conduit to provide palliation for patients with obstructing gastric carcinoma.

2. Experience in the use of such tubes in 15 patients is summarized, and technical points in their placement are described.

3. It is concluded that a tube of this design is a worthwhile palliative adjunct in patients with unresectable obstructing gastric cancer.

REFERENCE

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COMPLICATIONS IN 430 CONSECUTIVE PULMONARY RESECTIONS FOR TUBERCULOSIS

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IN PULMONARY TUBERCULOSIS the trends of postoperative complications have not deviated greatly except in occurrence rate from bronchopleural fistula, mixed and tuberculous empyema, and bronchogenic spread of disease. Mixed or tuberculous empyema and tubercular spread have decreased notably, largely because of the antimicrobials now available. Among the factors that have led to a decreased morbidity and mortality are the understanding of pulmonary physiology, improved anesthesia techniques, adequate transfusions, and greater experience in treating surgical complications. This survey was undertaken to review the complications encountered in pulmonary resection for tuberculosis performed at the North Carolina Sanatorium and to examine the methods used in treatment.

MATERIAL

During a 6 year period, from 1952 through 1957, 430 pulmonary resections were performed at the North Carolina Sanatorium, McCain, North Carolina. These resections were carried out by 13 surgical residents from Duke University Medical Center using essentially the same operative technique and postoperative care under the supervision of one of us (W.F.H.). To illustrate morbidity and mortality trends, the series was divided into consecutive groups of 215 cases each. Approximately one-half of these resections consisted of lobectomies including those associated with segmental or wedge resection. In the two groups the number of pneumonectomies and lobectomies was very similar. More segmental resections and fewer wedge resections were carried out in the latter part of the series (Table I).

This series was composed of patients who received antituberculous chemotherapy in general use at the time of the operation during the preoperative and postoperative periods. In most cases the drugs consisted either of isoniazid and para-aminosalicylic acid, or isoniazid and streptomycin, or occasionally all 3 drugs. In addition, in all cases the administration of penicillin was begun the day prior to operation unless contraindicated by a history of sensitivity. In the case of a sensitivity one of the broad spectrum antibiotics was substituted. Other chemotherapy, such as cycloserine, pyrazinamide, and viomycin, was not used unless clinical or laboratory studies indicated the patient's initial therapy was not effective. In patients with positive sputum or with bilateral disease, one or a combination of these latter drugs was added during operation. Pyrazinamide was used most frequently. The duration of additional drug treatment depended upon the residual disease, the presence of acid fast bacteria, and the progress shown by clinical and x-ray examinations.

RESULTS

Clarity of the terminology used in presenting the results is important. In order to avoid misunderstanding, the precise definition of terms follows:

Bronchopleural fistula. The development of air or air-fluid level in the pleural cavity

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TABLE I.—SURGICAL RESECTIONS (1952–1957)

Operation	40 months 1st 215 cases	32 months 2nd 215 cases	Total No.	Total Per cent
Pneumonectomy	19	13	32	7.5
Lobectomy	88	96	184	43.0
Lobectomy and segmental or wedge	25	19	44	10.0
Segmental	26	59	85	20.0
Segmental and wedge	5	10	15	3.5
Wedge	52	18	70	16.0
Total	215	215	430	

TABLE II.—BRONCHOPLEURAL FISTULA (45 CASES)

Operation	No. cases	B.P.F. Per cent	B.P.F. No.	Space problem, per cent	Drug resistance, per cent	Associated nontb. empyema, per cent	Postop. hemorrhage, per cent	Positive sputum, per cent	Proximal endobronchial disease, per cent
Pneumonectomy	32	28	9	—	23	23	11	11	11
Lobectomy	184	10	18	67	11	11	17	17	—
Lobectomy plus	44	18	8	38	38	25	13	13	—
Segmental	85	7	6	17	33	—	17	—	17
Segmental plus	15	27	4	25	—	—	—	—	—
Wedge	70		0	—	—	—	—	—	—
Total									
Per cent		10.5		47	20	13	13	11	4
No.	430		45	17	9	6	5	5	2

TABLE III.—COMPLICATIONS BY SURGICAL PROCEDURE

Operation	No.	B.P.F. per cent	B.P.F. No.	Hemothorax per cent	Hemothorax No.	Nontb. empyema per cent	Nontb. empyema No.	Disease spread per cent	Disease spread No.	Wound infection per cent	Wound infection No.	Brachial palsy per cent	Brachial palsy No.	P.O. psychosis per cent	P.O. psychosis No.	Totals per cent	Totals No.
Pneumonectomy	32	28	9	—	—	6.3	2	3.2	1	—	0	—	0			37.5	12
Lobectomy	184	10	18	4.9	9	1.1	2	2.2	5		0	0.5	1			18.7	35
Lobectomy plus	44	18	8		0	4.5	2		0		0		0			22.5	10
Segmental	85	7	6	2.3	2		0		0	1.2	1		0			10.5	9
Segmental plus	15	27	4		0		0		0		0		0			27	4
Wedge	70		0	10	7		0		0		0		0			10	7
Total																	
Per cent		10.5		4.2		1.4		1.4		0.2		0.2		0.9		18.7	
No.	430		45		18		*6		6		1		1		4		81

*All associated with B.P. fistulas.

signified the presence of a fistula. Often this was accompanied with expectoration of old blood. Also, a fistula was present if air continued to leak via intercostal catheter for more than 10 to 14 days and if an increasing pleural air space developed on clamping or removing the intercostal tube.

Space problem. This term was used in this presentation to describe the space in the hemithorax that the remaining lung failed to fill after resection. This problem was more frequent in patients with inelastic lungs, often secondary to emphysema and fibrous tuberculosis. Space problem and bronchopleural fistula were often associated but not synonymous.

Hemothorax. Patients with obliteration of one-fourth or more of the hemithorax by clotted blood were considered to have postoperative hemothorax. Instances of small apical collections of fluid or blood and excessive bleeding from the intercostal catheter were not included.

Empyema. All patients with this designation had clinical evidence of infection with purulent drainage positive on culture.

Disease spread. Irrespective of a patient's postoperative course, the spread of tuberculosis was determined by changes in the x-ray films. Sputum studies and the clinical course were not helpful since many patients had bilateral disease.

Wound infection. Small stitch abscesses were not included in this group. If the subcutaneous tissue was involved and drainage necessary, the complication was listed.

Operative and postoperative deaths were listed as a group. The postoperative ones included those occurring during the first 2 weeks after operation.

In 430 resections, 81 complications and 10 deaths occurred (Tables III and VI). The major complication, bronchopleural fistula, appeared in 10.5 per cent of the operative procedures. Fistulas developed in 28 per cent of the pneumonectomies. The majority of the fistulas following pneumonectomy occurred much later than those developing after the other types of resection. In those cases in which segmental resections and lobectomies plus a wedge or segmental resection were performed, the over-all fistula rate was 20 per cent (Table II).

Hemothorax developed in 4.2 per cent of the cases. Seven of the 18 cases followed wedge resection giving an incidence of 10 per cent. The 11 remaining cases followed lobectomies and segmental resections.

Nontuberculous empyemas were distributed equally among pneumonectomies, lobectomies, and lobectomies plus segmental and wedge resections. The empyemas were all complicated by a bronchopleural fistula.

Spread of tubercular disease was found in 6 patients. All were in the first half of the series. Five of the 6 disseminations followed lobectomies and the sixth occurred after pneumonectomy.

One infected wound occurred from which Staphylococcus aureus was cultured. Postoperative psychosis and brachial palsy were the other complications which are summarized in Table III.

Operative and postoperative mortality for pulmonary resection over the 6 year period was 2.3 per cent. The death rate in the first 215 patients was 3.7 per cent and decreased in the second 215 cases to 0.9 per cent (Table VI).

TREATMENT

The treatment of bronchopleural fistula and hemothorax is outlined in Tables IV and V. The majority of the bronchopleural fistulas were treated either by thoracoplasty or by conservative measures determined largely by the clinical progress, associated infection, and the size of the fistulous space. An intercostal catheter with or without suction was effectively employed in selected patients. Early in the series 5 operative closures of the fistulas were attempted, but all were unsuccessful. The majority of the 9 fistulas in the 32 pneumonectomies were treated conservatively by using antibiotics and optimum body position for drainage. In 5 of the 6 patients treated conservatively the evacuated space was obliterated within a period of 6 months to 1 year. In 3 of the 9 cases drainage and elective thoracoplasty for bronchial closure were later required. One patient refused thoracoplasty and has continued to have a large air space for over 1 year. Despite the presence of a fistula the patient has been asymptomatic during this period. In the remainder, a satisfactory closure of the fistula with a good result was obtained in 90 per cent of the cases. Pretreatment and posttreatment films reveal the results of the varied treatment (Fig. 1).

Postoperative hemothorax was treated in several ways, such as by varidase injections, repeated thoracentesis, decortication opera-

TABLE IV.—TREATMENT OF BRONCHOPLEURAL FISTULA (45 CASES)

Method	First 215 cases	Second 215 cases	Total No.	Total Per cent
Conservative	10	7	17	38
Thoracoplasty (with or without catheter)	3	13	16	36
Intercostal catheter (with or without suction)	2	4	6	13
Operative closures	5*	0	5	11
Thoracoplasty plus excision of fistulous tract and closure	1	0	1	2
Total	21	24	45	100

*All fistulas reopened and required another method of treatment.

TABLE V.—TREATMENT OF HEMOTHORAX (18 CASES)

Method	First 215 cases	Second 215 cases	Total No.	Total Per cent
Varidase irrigation	4	1	5	28
Decortication and operative evacuation	2	3	5	28
Conservative	2	1	3	17
Thoracentesis	4	0	4	21
Drainage via catheter	0	1	1	6
Total	12	6	18	100

TABLE VI.—OPERATIVE AND POSTOPERATIVE DEATHS (430 CASES)

Operation	1st 215 Cases		2nd 215 Cases		Total	
	Cases	Deaths	Cases	Deaths	Deaths	Per cent
Pneumonectomy	19	3	13	1	4	12.5
Lobectomy	88	4	96	1	5	2.2
Lobectomy and wedge or segmental	25	—	19	—	—	—
Segmental	26	0	59	0	0	0
Segmental and wedge	5	0	10	0	0	0
Wedge	52	1	18	0	1	1.4
Total						
No.	215	8	215	2	10	
Per cent		3.7		0.9		2.3

tive evacuation, and observation. The size and distribution of the clot were the principal factors involved in determining whether or not a closed or operative method of treatment should be carried out. In 1 patient a bronchopleural fistula became aggravated on treatment with varidase, and this treatment was abandoned. The over-all results using all other methods were satisfactory (Fig. 2).

All of the empyemas were nontuberculous and associated with a fistula. After culture and sensitivities of the causative agent were known, the appropriate chemotherapy was given. Spread of disease and wound infections were controlled with added antituberculous drugs and indicated antibiotics and drainage, respectively.

DISCUSSION

In the early resections performed before the advent of dependable antibiotic agents, the cause of complications and death consisted of progression of tuberculosis manifested by parenchymal spread, opening of the bronchial stump, or overwhelming empyema. Today the patient with an atypical or resistant organism may experience all these complications. In this study 12.6 per cent of the patients had either positive sputum smears or positive culture at the time of resection. One would have to assume that partial resistance to administered drugs existed as all patients were treated with an adequate dosage of drugs. In the past, hospital patients with positive sputum and resistant tubercle bacilli were often denied operation because of high morbidity. Early in this series, no patient with positive sputum was even considered for operation. In many patients, despite the high complication rate, this treatment offered the only chance for the sputum to be converted.

The causes of the morbidity and mortality could rarely be accounted for in patient selection or in a surgical technical error in this series. In 45 cases of bronchopleural fistulas 11 per cent of the patients involved had positive sputums and 20 per cent had shown drug resistance either clinically or by sensitivity test. Therefore, patients in whom fistulas developed had essentially the same incidence of positive sputums as the over-all group. A space problem per se was not considered a complication since a degree of space is always present after a resection. If the inelastic or diseased remaining lung did not expand to fill the pleural space, the possibility of fistula formation was greater. In approximately one-half of the fistulas, a space problem appeared as a precursor. The prevention of space problems by preresection or concomitant tailoring thoracoplasty for space obliteration in selected cases has been reported with enthusiasm. In 1955, there were a few cases in which resection and concomitant tailoring thoracoplasty were performed. Because of longer anesthesia time, added surgical trauma, increased blood loss, and increased postsurgical atelectasis, the patients in general had a stormy postoperative course. After these results this procedure was discontinued, and an elective 4 to 6 rib tailoring thoracoplasty was performed after resection when indicated. In the 6 cases of

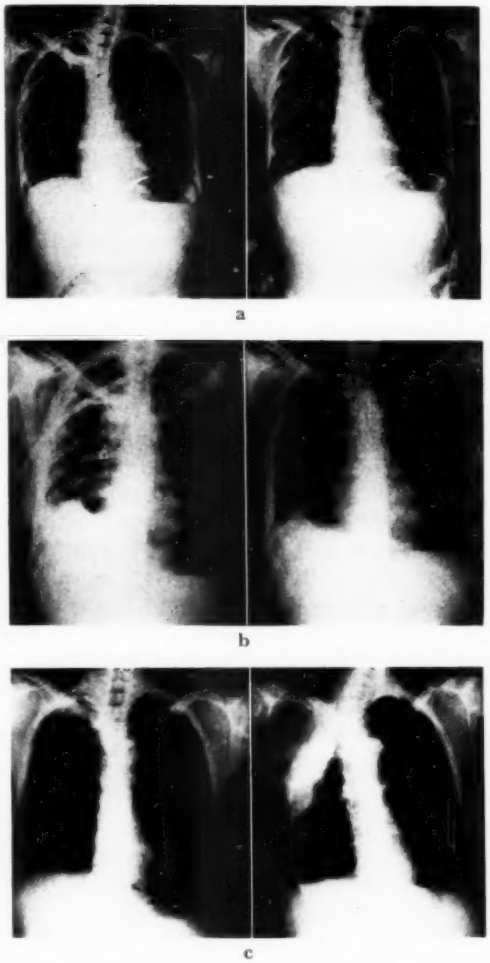

FIG. 1. Pretreatment and posttreatment films of bronchopleural fistulas. a, Conservative treatment b, Treatment with intercostal catheter. c, Treated by thoracoplasty.

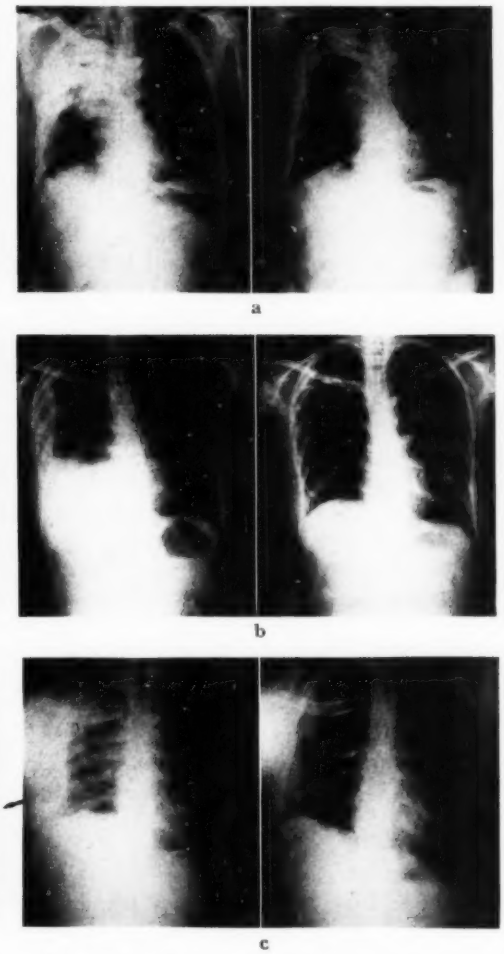

FIG. 2. Pretreatment and posttreatment roentgenographic films of hemothorax. a, Conservative treatment. b, Treated with varidase irrigations. c, Treated by decortication.

nontuberculous empyema associated with fistulas, it was impossible to determine whether the focus of infection was primary or secondary to the opening of the bronchus. Endobronchial disease near the proximal end of the bronchus or at the site of the bronchial amputation was seen in only 2 cases in which fistulas developed. In this group preoperative bronchoscopy in all cases was negative for endobronchial disease. The incidence of fistula formation was not decreased in the second 215 cases as compared to the decrease in other complications.

The complication of excessive bleeding during and after operation causing hemothorax was rarely due to a technical error. Tuberculosis involves not only lung parenchyma, but the pleura and often the chest wall. During resection by freeing multiple fibrous adhesions which are in various stages

of vascularization, many small vessels are divided. The ordinary retraction of the vessels is prevented as they course through the diseased pleura. Despite adequate hemostasis by ligature and cautery, in several cases oozing from raw surfaces continues. It is difficult to predict in which cases bleeding will not stop after closure. Even though the clotting mechanism is normal, bleeding may continue and fill the hemithorax. No deaths resulted from this type of hemorrhage.

The minimal occurrence of nontuberculous empyema, spread of tubercular disease, and pyogenic wound infection and the disappearance of tuberculous empyema were considered to be directly related to chemotherapy. In the last 215 cases no spread of tubercular disease occurred after surgery.

The operative and postoperative death rate was decreased significantly from 3.7 per cent in the first 215 cases to 0.9 per cent in the second 215 cases. Pneumonectomy continued to result in the highest mortality with an over-all 12.5 per cent. All deaths came during the postoperative period except 1 which followed hemorrhage during operation. The causes of death were varied and were not peculiar to this category of patients, consisting of: pulmonary insufficiency in 2 cases, pulmonary embolism in 2, operative hemorrhage in 2, cardiac arrest in 1, coronary thrombosis in 1, pulmonary edema in 1, and hepatic failure in 1.

SUMMARY

From a study of 430 consecutive resections for pulmonary tuberculosis, 81 significant complications and 10 deaths were found. The probable causes and treatment of the complications have been discussed. A bronchopleural fistula was the most common complication and occurred in 10.5 per cent of the resections. The over-all mortality rate was 2.3 per cent, but in the last half of the series the rate decreased to 0.9 per cent.

TRAUMATIC SEVERANCE OF PANCREAS TREATED BY ROUX-Y ANASTOMOSIS

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A STUDY of the reported experiences with the diagnosis and treatment of pancreatic injuries indicates that the handling of this problem has been unsatisfactory. This has been particularly true of that group associated with blunt trauma to the abdomen. Several classifications of pancreatic injuries have been proposed previously; however, for purposes of discussion, injuries of the pancreas may be classified as follows: (1) operative (due to surgery); (2) nonoperative, either penetrating injuries, or nonpenetrating injuries ("subcutaneous") (a) contusion or (b) laceration or fracture (without significant contusion or with contusion).

The present article is concerned with the nonoperative, nonpenetrating injuries, and in particular, the complete laceration or fracture of the pancreas.

Since Travers' initial brief report of a case of pancreatic injury, there have been occasional reports of trauma to the pancreas. Because of the relative infrequency of this type of injury, there has been no established or completely satisfactory method of handling these cases.

INCIDENCE

Due to the lack of extensive experience on the part of any one person or group, there is considerable discrepancy in the reported incidence of pancreatic trauma. The incidence of pancreatitis due to trauma has been estimated to be from 2 to 50 per cent of all cases of pancreatitis. One is impressed in reviewing the literature that most of those persons who have investigated this problem are of the opinion that these injuries occur more frequently than is commonly recognized. Waugh and Lynn attribute 6 of 58 cases of pseudocysts of the pancreas to trauma, and Connolly and Lempka estimate that 15 to 30 per cent of pancreatic pseudocysts are traumatic in origin.

The proportion of nonpenetrating to penetrating injuries of the pancreas is also subject to some diversity of opinion. Howard states that pancreatic injuries are seldom due to blunt trauma and are almost always due to penetrating injury. Most reports, however, indicate that the majority of known pancreatic injuries due to nonoperative causes are the results of blunt trauma.

Isolated injuries to the pancreas, in which there is no associated injury to other abdominal organs, have previously been considered to be rare; however, many reports indicate that isolated injury is not so uncommon.

ETIOLOGY

Pancreatic injuries due to nonpenetrating wounds are, apparently, the result of one of two mechanisms: (1) The pancreas may actually be caught between the striking force against the abdominal wall and the vertebral column posteriorly. (2) The damage to the pancreas may be the result of a contrecoup type of mechanism.

There has been considerable variety in the causative trauma of pancreatic injuries, although some reports indicate a high incidence of a particular type of injury common to a locale or practice. Reports from the military quite naturally have a high incidence of occupational injury. Reports from Texas by Culotta and associates and by Venable reveal a high proportion of injuries associated with horses and steers. Fallis and

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Barron have stated that a decrease in pseudocysts of the pancreas secondary to trauma is the result of the disappearance of the horse and buggy, while other reports implicate the steering wheel injury as a common etiologic mechanism. The most significant feature, however, of the etiology of pancreatic injuries is the extreme variability of the etiologic agent, and in particular the frequency with which seemingly trivial injuries may cause extensive damage to the pancreas.

DIAGNOSIS

Diagnosis, as to both the existence and the extent of pancreatic injuries, is difficult. It is seldom made preoperatively, and may even be unrecognized at the time of surgical exploration. Frequently, the first recognition of pancreatic disease is the finding of a pseudocyst several weeks after the causative injury.

The difficulty in diagnosis is principally due to three factors: (1) the variability of symptoms, (2) delay in onset of symptoms, and (3) masking by concomitant injuries.

The variability of symptoms may be marked and, as the nature of the injury, may be deceptively mild. Even with complete severance of the pancreas, there may be no more clinical evidence than mild abdominal pain. The variability and delay of symptoms and signs are apparently due to: (1) decrease in pancreatic secretion and increase in reparative response following injury as indicated experimentally by Popper and Necheles, (2) absence of an activating agent of the pancreatic enzymes in isolated injuries to the pancreas, and (3) the retroperitoneal location of the pancreas which may prevent spillage into the general peritoneal cavity with resultant peritonitis. Whatever the physiology of this reaction, it is most impressive to see a patient with a completely transected pancreas having minimal clinical findings for 48 hours when in other circumstances, death can result from necrotizing pancreatitis secondary to a small meticulous pancreatic biopsy.

When there are associated severe injuries, possible trauma to the pancreas may not be recognized, and this has been true even at laparotomy. The authors were impressed with the ease with which one of the injuries presented here might have been overlooked (Case 2).

While serum amylase determinations and peritoneal tap may, in some instances, be of aid, they will seldom provide a positive diagnosis and give no accurate indication as to the type and severity of the injury.

COMPLICATIONS

The morbidity, even more than the mortality, has been the major problem resulting from pancreatic injuries. Complications have, in the past, been an almost invariable consequence of severe pancreatic injuries.

Some degree of pancreatitis has practically always followed the injury. Pseudocyst frequently follows nonsurgical treatment, and fistula formation is the almost inevitable sequela of surgical intervention. Other complications resulting from pancreatic injuries are abscess formation, diabetes, calculosis and lithiasis, empyema and subphrenic abscess, and intestinal obstruction. Culotta and associates reflect the opinion in most reports, "With the exception of an occasional caudal amputation, it appears that little can be done to prevent the development of pancreatic complications, particularly fistulae and cysts."

Hemorrhage, apparently, is the most common cause of death in the early post-injury period.

TREATMENT

The diversity of opinion as to the proper place of operative and nonoperative treatment in the handling of these injuries is probably due to limited experience with a particular type of injury or injuries of a particular severity.

While the severity of the injury and the patient's general condition may in some cases limit the extent of surgery, it would seem that the approach to this problem has

TABLE I.—COMPLETE SEVERANCE OF THE PANCREAS

Investigator	*Injury*	*Operation*	*Complications*	*Result*
Becker	Complete severance of pancreas at the neck	Suture closure of the divided ends. Drainage	Fistula	Recovered after stormy course
Burnett	Complete severance at the mesenteric vessels	No repair. Drained	Fistula	Recovered
Estes *et al.*	Complete severance associated with other massive injuries	Injury to stomach and duodenum repaired. Pancreatic injury not recognized at surgery		Died
Flavell	Complete severance at the neck	Drainage	Fistula	Recovered
Hannon and Sprafka	Complete severance at the neck	Body and tail of pancreas excised. Splenectomy		Recovered
Hannon and Sprafka	Complete severance of the distal one-third of pancreas	Distal one-third of the gland excised. Splenectomy		Recovered
Hannon and Sprafka	Complete severance at the neck	Excision of the body and tail of pancreas. Splenectomy		Recovered
Kinnaird	Complete severance of the pancreas	Distal pancreatectomy and splenectomy		Died
Venable	Complete severance of the tail	Unable to suture the gland. Drained		Died
Brown and Barlow	Complete severance of the pancreas	Ends of the glands were approximated with suture (duct not repaired)	Fistula	Recovered
Kerr	Complete severance in the middle of the pancreas	Ends of the gland were approximated with suture (duct not repaired)	Fistula	Recovered
Newton	Pancreas severed at neck	Severed ends closed with suture. Drained	Cyst and fistula	Recovered
Smith	Complete severance of the pancreas	Approximation of the ends of gland with sutures	Cyst	Recovered
Travers	Complete transection of the pancreas with laceration of the liver	None (found at autopsy)		Died

been unduly pessimistic and conservative. There has, in comparison to other surgical problems, been a lack of definitiveness in the handling of these injuries.

SEVERANCE OF THE PANCREAS

The lacerated or severed pancreas is the most amenable of the pancreatic injuries to definitive surgical treatment. While repair of the injured duct and suture of lacerations has been recommended, it has rarely been successfully practiced.

The instances of recognized and adequately described cases of complete severance of the pancreas found in the literature are listed in Table I. It is of interest that a study of other reports of pancreatic injury lead one to suspect that some of these represent a severance which was not recognized, even in retrospect.

It is apparent in studying Table I that with 1 exception, the methods employed have resulted inevitably in cyst or fistula formation or death. Only excision of the distal fragment with a technically necessary concomitant splenectomy as used by Hannon and Sprafka has avoided the complications previously encountered. This method does, however, entail the loss of functioning pancreatic tissue. While much of the pancreas may be excised in most instances without resulting pancreatic deficiency, the functional reserve of the pancreas is not accurately known. If a considerable portion of the gland is removed, diabetes will occasionally result. Marshall reports 2 instances of

FIG. 1. This is an illustration of the almost identical findings noted in both Cases 1 and 2 with the pancreas completely divided and the ends retracted with exposure of the superior mesenteric vein and with the splenic vessels intact.

the development of diabetes following partial pancreatectomy for hypoglycemia in a series of 18 patients surviving surgery. Also, enzyme deficiency, while less easily recognized or measured, is highly undesirable. Certainly, preservation of the entire pancreas is desirable if other complications can be avoided.

The authors have recently employed a previously unreported and what is believed to be a more definitive operation in the management of complete severance of the pancreas. It allows preservation of the pancreatic tissue while providing for the pancreatic secretions, and it has avoided the complications previously encountered. The principal possible objection might be the extensiveness of the procedure; however, it is hardly more time-consuming than resection of the distal fragment which requires the additional procedure of splenectomy. The following 2 cases are presented for illustration:

CASE 1. B. C. (service of Richard Gray, now of Rome, Georgia), a 20 year old white female, was admitted to Grady Memorial Hospital on June 29, 1957, shortly after being involved in an automobile accident. Her chief complaint was pain in the right upper quadrant and costovertebral angle. She had some nausea and a feeling of faintness. Initially her blood pressure was 110 millimeters of mercury systolic and 65 millimeters of mercury diastolic, but during the short stay in the emergency clinic, the blood pressure dropped to a systolic of 90 millimeters of mercury and a diastolic of 70 millimeters of mercury with her pulse rate increasing to 90 per minute. She vomited a small amount and fainted twice while in the x-ray department.

There were some minimal lacerations of the lip, but the remainder of the examination was negative except for the abdominal findings which consisted of mild, generalized tenderness with the pain maximal in the epigastrium and the left upper quadrant. There was no muscle rigidity. Some rebound tenderness was present. No masses could be palpated, and the sounds of peristalsis were normal. Urinalysis was reported as negative. Roentgenograms of the abdomen and chest were interpreted as normal. Hemoglobin was reported as 10.8 grams per cent. The tentative diagnosis was possible fracture of the liver or spleen. An immediate laparotomy was recommended.

At operation there was no evidence of any abdominal injury other than the pancreas. On examination of the pancreas it was found to have a complete, transverse severance at the neck, directly overlying the superior mesenteric vein. The mesenteric vessels were lying exposed, and the splenic artery and vein were intact. There were approximately 1,000 cubic centimeters of free blood in the abdominal cavity. The procedure undertaken was as illustrated. The distal end of the head of the pancreas was closed with interrupted figure-of-8, No. 4-0 black silk sutures, after identification and ligation of the distal end of the duct of Wirsung. The proximal end of the distal fragment, that is the body and tail of the pancreas, was freed for a distance of a little over 1 centimeter with great care taken not to tear the splenic vessels. The jejunum was then divided at a point about 14 inches below the ligament of Treitz, and a Roux-en-Y pancreatojejunostomy was accomplished by implanting the severed end of the pancreas in the defunctionalized segment of jejunum with 2 tiers of interrupted, No. 4-0 black silk sutures. A Penrose drain was exteriorized through the left flank, and a sump drain was placed near the anastomosis and exteriorized through the incision. The abdominal wall was closed, using No. 32 stainless steel wire sutures. The patient received 4 pints of blood during surgery. Her condition immediately after operation was good.

On the first postoperative day, the patient's urinary output was good, and her fluid transfer was in balance. The laboratory reported her hemoglobin as 14.0 grams per cent, and her leucocyte count was 28,850 cells per cubic millimeter with 89 per cent being polymorphonuclear leucocytes. On the second postoperative day the carbon dioxide combining power, chloride, sodium, and potassium of the serum were normal. On auscultation some sounds indicative of hypoactive peristalsis in the abdomen were heard. On the following day these sounds indicated normal peristalsis. The Levin tube and the Foley catheter were then removed, and the patient was given surgical

liquids. Except for 1 episode of vomiting on the fifth postoperative day, the patient had no difficulty. Blood sugar determinations on the fourth and sixth postoperative days were 86 and 81 milligrams per cent respectively. By the eighth postoperative day, a few cubic centimeters of fluid were obtained by the sump drain, and on the twelfth day after surgery this drain was removed. On the thirteenth postoperative day, the laboratory reported the serum amylase to be 23 Bodansky units, the hemoglobin 13.9 grams per cent, and the leucocyte count 14,150 cells per cubic millimeter. The patient was afebrile and ambulatory and was discharged from the hospital on the fourteenth postoperative day.

The patient was followed up closely in the outpatient department. There was some complaint of nausea and vomiting on 2 occasions, but they, apparently, were minor episodes. Five months after discharge, a gastrointestinal x-ray series was reported as "negative." On October 24, 1957, she had no evidence of disease. The patient, subsequently, was found to have a carcinoma in situ of the cervix for which she has been treated. She was seen recently, 14 months after her pancreatic injury, at which time she was asymptomatic.

CASE 2. M. S. H., a 10 year old white female, was admitted to the Georgia Baptist Hospital on May 25, 1958. She had a history of having fallen while riding a bicycle 2 days previously and having been struck under the left ribs by the handle bars. She was hospitalized elsewhere and had been observed for a 48 hour period of time, during which time the leucocyte count rose from 12,000 cells per cubic millimeter to 17,000 cells per cubic millimeter, and the abdominal pain and tenderness had increased. She had developed some nausea and vomiting. At the time of admission, physical examination was essentially negative except that the abdomen was full and tender with exquisite tenderness in the epigastrium. There was some dullness to percussion on the left side, and the sounds of peristalsis were subdued. At that time the white differential blood count was reported to have 94 per cent polymorphonuclear leucocytes, the hematocrit 40 per cent, and the hemoglobin 12.7 grams per cent. Sugar in the urine gave the reaction of 4 plus, but this was thought to be due to an intravenous clysis of glucose which the patient was receiving at the time of voiding, for the blood sugar an hour later was normal. The serum amylase was not done at this time. The patient was thought to have a subcapsular, ruptured spleen, and an exploration of the abdomen was done.

At operation this patient was found to have no abnormalities in the abdomen except the presence of several hundred cubic centimeters of serosanguineous fluid in the peritoneal cavity. There were also several small yellow areas of fat necrosis, and a soft mass was palpable in the retrogastric area. Upon opening the lesser peritoneal sac, the midportion of the pancreas was obscured by a rounded, edematous area. No fistulous opening could be identified, but because pancreatic enzymes must have escaped, a fact recognized by the areas of fatty necrosis, this area was opened by blunt dissection. Under the edematous tissue, which in reality was the beginning of a pseudocyst, the pancreas was found to have suffered a complete, transverse severance at the neck. This could very easily have been overlooked. The mesenteric and portal vessels were exposed, and the splenic vessels were intact. A procedure, similar to that in Case 1, was carried out, the closure of the distal severed end of the head of the pancreas, and placement of the severed end of the body of the pancreas into a defunctionalized loop of jejunum with a Roux-en-Y anastomosis as in Figure 2. The anastomosis and closure was executed with interrupted No. 4-0 blue cotton sutures. A sump drain was placed near the area of the pancreatic injury and exteriorized through the abdominal wall, which was closed anatomically using cotton sutures. The patient's condition immediately after the operation was good.

FIG. 2. A Roux-Y type of pancreatojejunostomy has been made with the caudal portion of the pancreas and the defunctionalized jejunum. The posterior end of the head of the pancreas has been closed with interrupted sutures. Inset shows the technique of the anastomosis.

On the third postoperative day, the patient was ambulatory, and since the sounds of peristalsis appeared normal, the Levin tube was removed. The patient was given a low fat diet to eat. On the ninth day after surgery the sump drain was removed, and the patient was discharged from the hospital. During her hospital stay, her blood sugar determinations on the

day of surgery, the first and third postoperative days, all were within normal limits. Blood chemistry consisting of carbon dioxide combining power, potassium, sodium, and chlorides of serum were all within normal limits.

The patient's subsequent course has been quite satisfactory. She has had no difficulty since surgery.

Each instance of injury to the pancreas must be evaluated and handled according to its own characteristics, and no single method of dealing with this problem will satisfy all cases. A more definitive and specific approach to all should, however, improve the results of treatment. The technique described is a definitive approach which should be applicable to severance of the pancreas, whether due to blunt or penetrating trauma, with gratifying results. No reference to this method of treating severance of the pancreas is found in the literature.

SUMMARY

1. Injuries to the pancreas are more common than generally recognized. They are due to a variety of types of trauma, and in particular to blunt trauma, often of a character which may appear to be insignificant.

2. Treatment of these injuries in the past has been unsatisfactory, and practically always associated with complications, in particular cyst and fistula formation.

3. Complete severance of the pancreas in particular provides an opportunity for a more definitive treatment of these injuries. A previously unreported technique employing the Roux-Y anastomosis is described in this article.

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COMPENSATORY MECHANISMS FOLLOWING MASSIVE SMALL BOWEL RESECTION FOR INTESTINAL VOLVULUS

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RESECTION of a large portion of the small intestine is always a dramatic and often a catastrophic event. In recent years with improved anesthesia, more effective antibiotics, and blood replacement therapy the mortality rate has fallen sharply for massive small bowel resection, and the surgeon and clinician are more commonly confronted with the problem of the patient from whom a large amount of the small intestine has been removed and the management of the resulting insufficiency.

Experience has shown that a patient can withstand the resection of at least 33 per cent of the small intestine and expect normal digestive function; 50 per cent removal constitutes the upper limit of safety, and resection above 50 per cent of the small intestine frequently results in severe nutritional problems and often in the death of the patient. Many reports of successive resection of 200 centimeters or more of the small intestine are found in the literature but the exact mechanisms by which the patient with a markedly shortened small intestine is able to maintain normal nutrition and fluid and electrolyte balance are poorly understood.

Elongation of the passage time of fluid through the remaining small bowel has been suggested by West and associates as one possible mechanism for increasing the absorption of various nutrients from the intestinal contents. Others have suggested that the small bowel increases its absorptive surface by lengthening and by increasing in circumference. Still other workers have suggested that "intestinalization" of the portion of the colon on the right side occurs in patients who survive massive small bowel resection.

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In 1938 West, Montague, and Judy reviewed their studies of a man in whom all of the small intestine but 3 feet had been resected. The remaining small bowel dilated and hypertrophied to the size of a normal colon. This patient, however, had tetany, low serum calcium, and extremely poor nutrition. His protein and fat absorption was markedly impaired. Jackson, Linder, and Berman (2, 3) extensively studied a young Italian male who survived resection of all but 7 inches of the jejunoileum performed for volvulus. This patient had recurrent absorption difficulties and required repeated hospitalization for vitamin and protein replenishment. He ultimately died in a severe deficiency state, and at autopsy some thickening of the wall of the duodenum and jejunum was noted but the ileum was not enlarged. There was some question of hypertrophy of the remaining small intestine and this difference of opinion could not be resolved. Althausen and associates reviewed 2 cases of massive resection. It was their opinion that the adaption mechanism occurring after massive resection involved three separate phases: (1) The patients almost universally lost weight thereby reducing caloric requirements and protein replacement requirements. (2) There was an expanded absorptive capacity of the remaining bowel by enlargement and thickening of the bowel. (3) "Intestinalization" of the colon occurred.

In the past 8 years 4 patients have been observed with volvulus of the small intestine in whom massive small bowel resections were required. All 4 patients survived the procedure and were successful in compensating for the loss of a large segment of the small intestine and in maintaining normal nutrition and fluid and electrolyte balance. One

of these patients presented a unique opportunity for periodic re-examination of the remaining small intestine and colon to determine whether enlargement or thickening occurred in the small intestine and whether any gross changes occurred in the colon subsequent to the massive resection.

A 21 year old white female underwent massive small bowel resection February 15, 1953 for volvulus and massive gangrene of the small intestine. The patient was pregnant at the time, and approximately 400 centimeters of the small intestine were resected. The remaining small intestine, extending from the ligament of Treitz to the ileocecal valve, was 42 inches in length at the time of operation. Four inches of the remaining bowel consisted of terminal ileum and the rest was proximal jejunum. The patient withstood the operative procedure and rapidly compensated for the loss of a large portion of the small intestine.

Seven months postoperatively cesarean section was necessary because of gross pelvic bony abnormality and the author was offered the opportunity of re-examining the bowel at that time. Measurement revealed the small bowel to be 40½ inches in length, and the bowel was perhaps slightly enlarged in diameter but definitely not in length. The colon appeared normal with no changes in size, shape, or consistency. The patient had one bowel movement daily at that time and there was no difficulty in nursing the child.

Approximately 1 year after operation the patient again became pregnant, and on September 14, 1954 (19 months postoperatively) she again had cesarean section with delivery of a normal child. The bowel at that time measured 43 inches in length. It was normal in diameter and color. Serum calcium studies on both the mother and child revealed no abnormalities in calcium absorption. The patient continued to have no diarrhea or difficulties as long as she avoided excess fatty intake.

In 1957 the patient again became pregnant, and on October 20, 1957 (56 months postoperatively) a third cesarean section was performed and a normal child was delivered. The small bowel was examined, photographed, and measured. It measured 41 inches from the ligament of Treitz to the cecum. The bowel showed no marked change in thickness or diameter and the colon appeared normal in every respect.

Finally on August 25, 1958 (66 months postoperatively), cesarean section was performed for the fourth time and a normal child was delivered. The small bowel measured 45 inches in length and there was no enlargement in diameter or thickening noted at this time.

This patient has demonstrated clearly that successful adjustment may be made by the remaining small intestine following massive resection of a large portion of the small gut. She has failed to exhibit any abnormal absorption mechanism and has successfully been carried through 4 pregnancies and 4 celiotomies without any marked alteration in her protein or electrolyte balance. This patient weighs approximately 130 pounds at the present time which is 5 to 10 pounds more than prior to the original operation.

The possible mechanisms by which compensation has occurred for the tremendous loss of absorptive surface in this patient are interesting. The thesis that massive small bowel resection is frequently followed by loss in weight so that caloric requirement and protein replacement requirement are reduced is not substantiated by this case. It would seem that the remaining small intestine has increased its efficiency tremendously but this has not been accomplished by increasing the amount of absorptive surface exposed to the intestinal content.

It seems probable that there is a large margin of safety in the amount of small bowel surface available for absorption. Thus a large proportion of the small bowel may be removed or diverted from the intestinal stream and adequate absorption will still occur. Certainly similar examples of excesses of functioning tissue can be found in other portions of the body; thus one kidney may be removed with no marked alteration in the excretory efficiency of the body. The body can withstand resection of large portions of the liver without any measurable change in liver function as we now measure it. It is likely that no compensatory changes must occur in the small intestine unless the remaining segment is overtaxed in its absorptive function.

The intolerance to fats and fatty foods which is noted in almost all patients with massive bowel resection is perhaps an exception to this general principle. The intestine is less efficient in absorbing fats than in absorbing proteins and carbohydrates, and accordingly a larger absorptive surface is necessary for the complete utilization of fat. Thus the patient who has lost a large portion of the small intestine will have a relative intolerance for fats and fatty foods and will notice diarrhea or bloating as the undigested

fat passes through the small gut into the colon producing some local irritation in this organ.

SUMMARY

It has been postulated by numerous authors that following massive small bowel resection the body compensates for the loss of a large proportion of its intestinal absorptive surface by various means. Some have suggested that the remaining bowel enlarges so that there is increased size and thickness with expanded absorptive capacity, that the patient loses weight so that there is reduced caloric and protein requirement, and finally that probably "intestinalization" of the colon occurs to compensate for the loss of absorptive surface. Others have described patients with massive small bowel resection who ultimately died in marked deficiency status and in whom the bowel was tremendously dilated and thickened.

It seems likely that nature has provided a large factor of safety in the amount of available absorptive surface in the small intestine. Today man eats highly concentrated foods with small bulk content, and it is possible that he requires less than half of the available absorptive surface to utilize adequately the foods which he ingests. Under such circumstances no compensatory mechanism is required if approximately half of the small intestine is removed and no dilatation, intestinalization, or reduction in over-all caloric and protein requirements is necessary to explain the method by which such an individual survives and enjoys good health. Thus, as long as the absorptive capacity of the small intestine is not overloaded by demands of the body for adequate nutrition or by excessive food intake, no compensatory mechanism must be postulated. Under these circumstances one would anticipate that the bowel would not change in size or appearance. If, however, the absorptive capacity of the remaining small intestine was impaired by underlying disease, or if the remaining segment of small intestine was too small to maintain the patient adequately, then the body would attempt to compensate for this by dilatation, lengthening, and certainly reduction in the size and weight of the patient.

If massive bowel resection is required and the remaining segment of bowel has a normal absorptive capacity, no compensatory mechanism comes into play as long as the factor of safety is not exceeded. At least 50 per cent of the small bowel may be removed in the majority of patients without any marked alteration in their absorptive efficiency.

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THE PROGNOSTIC SIGNIFICANCE OF ELECTROLYTE AND WEIGHT STUDIES IN CONGENITAL HYPERTROPHIC PYLORIC STENOSIS

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SINCE FIRST DESCRIBED in 1912, the Fredet-Ramstedt pyloromyotomy has been the standard operative procedure used in the treatment of pyloric stenosis. The literature implies that treatment and recovery are routine and generally uncomplicated. They are in the majority of cases; however, vomiting and poor weight gain occasionally persist in the postoperative period. A review was undertaken to determine if there were any preoperative signs by which prediction might be made of a child's course after pyloromyotomy. This study is based on an analysis of 349 consecutive cases of infants with congenital hypertrophic pyloric stenosis who were treated surgically at the Children's Hospital of Pittsburgh from 1947 to 1957.

GENERAL ANALYSIS

The traditionally observed preponderance of males over females in pyloric stenosis was noted in this series. Eighty per cent of the patients were males. Considering the rather large proportion of negro patients seen at the clinics of the Children's Hospital of Pittsburgh, the incidence of pyloric stenosis in that race was a surprising 3.7 per cent.

As can be seen in Figure 1, the diagnosis of pyloric stenosis was made between the age of 3 and 4 weeks in over 40 per cent of the admissions in this group. This is a less classical peak incidence than others have written about.

Emphasis is always placed on pyloric stenosis being a disease predominantly found in the first child. The significance of birth rank has been challenged by some authorities on the basis that the average American family has only 1.5 children. In this series, 46 per cent of the infants were noted to be first born, 27 per cent were second born, and 27 per cent were third born or later. The incidence of pyloric stenosis in twins was no greater than in the general population.

Several instances were noted in which 2 or more members of the immediate family had pyloric stenosis. In one family, composed of 3 boys and 1 girl, all had had pyloric stenosis.

Forty-four per cent of the infants were noted to have the first and most important symptom of pyloric stenosis—vomiting—between the ages of 2 and 4 weeks. Contrary to popular teaching, the onset of vomiting before this age was not uncommon, since 31 per cent began vomiting between the first and fourteenth days of life. Emesis may begin late, as in 1 infant who first vomited at 3 months of age and in whom the diagnosis was not established until 5 months of age.

Bile was seen in the vomitus of 2 patients. Blood was noted as part of the emesis in 3 children, probably representing the result of persistent vomiting with a small vessel rupturing.

PHYSICAL EXAMINATION

Although the presence of visible gastric waves along the upper abdominal wall is not pathognomonic of pyloric stenosis, it is a

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finding of importance. They were definitely observed in 79 per cent of our patients. The sign of greatest diagnostic significance is the palpation of a pyloric tumor. In 90 per cent of the patients reviewed, a tumor was palpated, in 7 per cent it was not, and in 3 per cent a questionable tumor was noted. If the tumor is not palpable, at least one authority defers surgical intervention. In such instances, surgery is still indicated if an upper gastrointestinal series reveals the classical picture of pyloric stenosis. Such a condition is found more commonly in infants under the age of 2 weeks, since generally speaking, the younger the child the smaller the tumor will be.

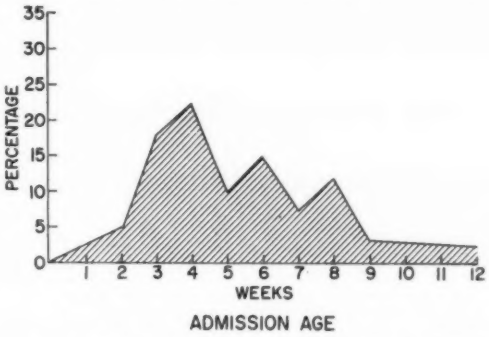

FIG. 1. The percentage of children admitted at various ages.

STUDIES

It has been said that the average birth weight of infants with pyloric stenosis probably does not vary from the normal. Twenty-eight per cent of this series weighed between 6 and 6.9 pounds at birth, 40 per cent weighed between 7 and 7.9 pounds, and 19 per cent weighed between 8 and 8.9 pounds.

It is obvious that those infants with obstruction will weigh less preoperatively than normal children of a similar age. In this study, it was found that 28 per cent of the infants had lost between ½ and 2 pounds from their greatest attained weight. Forty-six per cent did not lose weight but simply failed to gain weight, leaving only 26 per cent who gained normally.

Diagnostic x-ray examination was performed in 25 per cent of the total series. A thin barium mixture was used in any infant in whom palpation of a definite tumor was uncertain and gastric waves could not be demonstrated. Pyloric tumors were found in all patients who had x-ray findings diagnostic of pyloric stenosis.

In recent years, the determination of serum electrolytes has been standard procedure in all patients with pyloric stenosis. Sodium, chloride, potassium, and carbon dioxide levels were obtained in 257 (73 per cent) of the total cases. Of this group, 95 (37 per cent of those having chemistry determinations) were found to have alkalosis. Patients were classified as mildly alkalotic when the carbon dioxide level was between 29 and 32 milliequivalents per liter and the chloride ions were between 80 and 90 milliequivalents per liter. Moderate alkalosis was so defined when the chloride ions were between 70 and 80 milliequivalents per liter and the carbon dioxide level between 32 and 35 milliequivalents per liter. Severe alkalosis was applied to that group whose serum chlorides were under 79 milliequivalents per liter and whose carbon dioxide content was greater than 35 milliequivalents per liter. Figure 2 shows the series incidence of alkalosis under these three categories.

TREATMENT

The great majority of operations were performed by 4 members of the surgical staff, or residents under their supervision.

Fifty-three per cent of the patients were hospitalized for 24 hours before surgery,

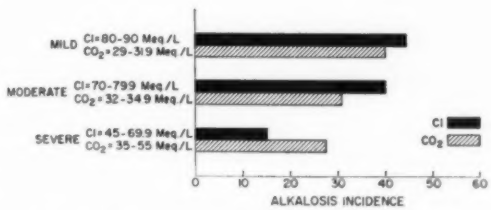

FIG. 2. The incidence of mild, moderate, and severe alkalosis encountered in this series.

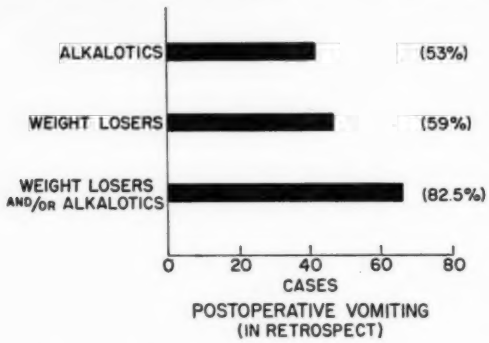

FIG. 3. The number of patients vomiting postoperatively who were alkalotic, lost weight, or had a combination of these conditions preoperatively.

with routine evaluation of electrolytes; none of these needed reconstitution and were considered the "normal" group. Forty-seven per cent needed 2 or more days of preparation for surgery. Most of these were alkalotic or had had extended trials of drug and "formula-change" therapy. Thirty-five per cent of this latter "abnormal" group took 2 days of reconstitution and 12 per cent needed 3 or more days. After calculation of extracellular and intracellular deficits from serum electrolyte determinations, blood, glucose, sodium chloride, and potassium chloride were used intravenously in their reconstitution.

The Fredet-Ramstedt pyloromyotomy was routinely done, using either a right rectus retracting or a transverse incision. The operating time was under 30 minutes in 41 per cent and between 30 and 40 minutes in 35 per cent of the cases. Two out of the 349 patients required reoperation because of incomplete myotomy, and both of these patients did well after the second procedure. The first of these patients was operated on at age 11 days and reoperated upon at 23 days of age. The second patient was 2 months old at operation and was reoperated upon on the tenth postoperative day.

A number of postoperative feeding regimens were utilized without significantly different results.

POSTOPERATIVE VOMITING

In more cases than realized, postoperative vomiting is a cause for concern to attending physicians. With the exception of some recent articles, little has been said in the literature regarding this problem. Giuseffi predicted that patients 6 weeks of age or older had a greater tendency toward a stormy postoperative course. This observation was not confirmed in this series; in fact, postoperative vomiting was perhaps slightly commoner in infants 2 to 3 weeks of age. Pollock and associates report that about 36 per cent of their patients vomited more than 7 times postoperatively, while Nicholson's group noted that over 20 per cent vomited for 5 or more days after surgery.

Any vomiting in excess of 3 times per day, or that lasting longer than 5 days after surgery, placed a patient in this series in the group of postoperative vomiters. Eighty out of 349 patients (23 per cent) had such moderate to severe emesis. In retrospect, 42 of the 80 patients (53 per cent) were definitely alkalotic. Forty-seven (59 per cent) of the vomiting group had significant preoperative weight loss. Fourteen of the 80 vomiters (17.5 per cent) had neither alkalosis nor significant weight loss, leaving 66 (82.5 per cent) who had vomiting associated with alkalosis or weight loss. Figure 3 portrays this retrospective analysis of the vomiters.

Since this study was undertaken to determine if there was any preoperative indication as to which patients might vomit after surgery, our data were analyzed in 3 other ways.

Of all the patients in the series, 98 (28 per cent) lost significant weight preoperatively and 251 (72 per cent) did not. Among those who lost weight, there were 47 postoperative vomiters, an incidence of 48 per cent; the vomiting incidence among nonweight losers was 13 per cent.

There were 95 patients with alkalosis in the total series. Of these, 42 (44 per cent) were in the postoperative vomiting group; only 14 of the 162 patients without alkalosis vomited—an incidence of 9 per cent.

Finally, in the whole group of 129 patients who had preoperative alkalosis or weight loss, one could predict an incidence of 51 per cent vomiters postoperatively. By contrast, among the remaining 220 patients who were nonalkalotic and had no weight variation, the incidence of vomiting was only 6 per cent.

Figure 4 summarizes these data and shows that if a patient has weight loss or alkalosis his chances of having postoperative emesis is 3 to 8 times greater than a patient without these aberrations.

In the past, two other factors have been incriminated as causes for postoperative vomiting. The first of these was the possible etiologic relationship of a preoperative gastrointestinal series. In the years from 1952 to 1957, 82 of 198 operative patients had a preliminary x-ray examination, while only 4 out of 151 had one between 1947 and 1951. In the 1952 to 1957 period, 55 patients vomited, whereas 25 patients in the earlier group did. However, when analyzed closely, this apparent preponderance of vomiters during the time more x-ray examinations were done does not hold up; the vomiting was equally present among patients who did and did not have gastrointestinal series.

The second factor suspected in postoperative emesis was duration of surgery. During the entire period studied in this series, 141 operations took less than 30 minutes with 16 per cent vomiting postoperatively. One hundred and twenty-one operations consumed 30 to 45 minutes with 26 per cent vomiters, and 82 operations exceeded 45 minutes' duration with 30 per cent vomiting after surgery. No conclusions can be drawn from this second factor studied, except that it would seem that the longer the surgery the more chance of vomiting. This may simply reflect that longer operations require more tissue handling, with more difficulties encountered.

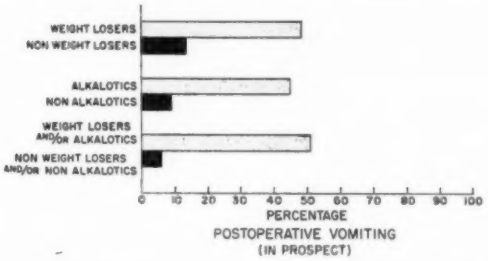

FIG. 4. Percentage incidence of postoperative vomiting in children who had lost weight, were alkalotic, or had a combination of these two conditions preoperatively. This is compared in each case to the incidence of vomiting in nonweight losers, nonalkalotic, and normal children.

COMPLICATIONS

Duodenal perforation at the time of surgery is not an unusual occurrence, at least according to Giuseffi. Untoward effects from this complication are negligible if the error in technique is recognized and corrected at the time of surgery. Ten such perforations (2.9 per cent) occurred in this series, and perfectly smooth postoperative courses were observed in all. In these cases, a nasogastric tube was inserted after surgery and the patient was not fed orally for 24 to 48 hours.

The remaining postoperative complications numbered 29, and in order of frequency were: wound infections, diarrhea, evisceration, and pneumonia.

RESULTS

It is well known that the mortality rates in patients operated upon for pyloric stenosis have dropped markedly in the last 20 years. Donovan reported an 0.8 per cent mortality rate in 1946, compared to 5.9 per cent up to 1932; Benson has recently reported a 0.6 per cent mortality.

There were 3 postoperative deaths in this series, a 0.9 per cent mortality rate. One death was due to aspiration pneumonia, while a second death was due to pneumonia with severe electrolyte imbalance. The third death occurred 2 weeks postoperatively and was characterized by sudden, massive upper gastrointestinal hemorrhage; autopsy revealed that the patient had a large gastric ulcer on the greater curvature, pneumatosis of the entire ileum, and cerebral edema.

Follow-up studies were attempted on four groups of patients: (1) all postoperative vomiters, (2) all preoperative alkalotic patients, (3) all patients who lost significant weight preoperatively, and (4) a group of random patients who neither vomited nor were alkalotic but might have had preoperative weight loss.

Because of considerable overlap in the groups, the total follow-up was on 100 patients. All 100 patients gained from 1 to 4 pounds in the first postoperative month at home. The average gain was about 2 pounds per child. Only 5 patients had occasional regurgitation for 1 to 2 months after leaving the hospital; all of these were patients who were in the category of postoperative vomiters at the time of their hospitalization. The remaining infants progressed as normal children.

SUMMARY

A series of 349 consecutive cases of pyloric stenosis, treated by pyloromyotomy with an 0.9 per cent mortality, has been reviewed.

One can prognosticate a 3 to 8 times greater incidence of postoperative vomiting among patients having preoperative alkalosis or loss of greater than one-half pound in weight when compared to the group showing normal values.

Duration of surgery seemed to have a bearing on postoperative vomiting, since the incidence of vomiting was twice as great in those patients whose operations required more than 45 minutes as in those taking less than 30 minutes.

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SOME EPIDEMIOLOGIC CONSIDERATIONS OF THROMBOEMBOLISM

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CERTAIN epidemiologic factors have frequently been neglected as an aid in the diagnosis, plan of treatment, and in an approach to prevention of thromboembolic disease. In a prior phase of this study (7) we have described the vagaries in the clinicopathologic manifestations of pulmonary embolism. The high frequency, clinical significance, and difficulties in diagnosis and treatment were stressed. During a 10 year period almost 14 per cent of all patients coming to postmortem examination had pulmonary emboli; in only 7 per cent of those patients with pulmonary embolism was a definitive diagnosis made prior to death.

The clinical manifestations of thromboembolism (both deep venous thrombosis and pulmonary embolism) are usually so vague and nonspecific that any additional information one may obtain regarding the relative risk of pulmonary embolism in a given individual may be of some aid to the clinician in making a decision with regard to the diagnosis in a particular patient. In addition, the presence of one or more factors predisposing to thromboembolic disease may influence the choice of length of anticoagulant therapy necessary to prevent extension of the venous thrombosis or a recurrent episode of pulmonary embolism. We also hope that greater knowledge of those factors and diseases associated with an increased frequency of thromboembolism will encourage the clinician to adopt more frequently a program of prophylactic anticoagulants in selected patients carrying a high predisposition to the development of thromboembolic complications.

Many autopsy studies of pulmonary embolism reported in the past have used an invalid approach to the evaluation of epidemiologic factors. A group of patients who were found at necropsy examination to have pulmonary embolism were selected. A certain percentage of those patients with pulmonary embolism were recorded as having heart disease as well, or cancer, or to be in a certain age group; these percentage figures are of very limited value unless one knows the distribution of these diseases and factors in the entire autopsy population without pulmonary embolism. The important consideration is not how many patients with pulmonary embolism have heart disease, but, rather, what is the incidence in the entire autopsy population of pulmonary embolism in all patients with heart disease as contrasted to its incidence in all the patients without heart diseases. Thus one obtains an *absolute* incidence of pulmonary embolism in the two groups and can contrast the relative risk of pulmonary embolism in each group. This is the approach which we have attempted to utilize whenever possible.

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METHODS

All autopsies performed at the University of Michigan Hospital over the 10 year period from January 1, 1945 through December 31, 1954 were individually reviewed. Only incomplete autopsies and stillbirths were excluded from the study. Mean autopsy rate over the entire 10 year period was 68.6 per cent. The selection of cases of pulmonary embolism was restricted to those emboli of thrombotic origin, excluding fat and carcinoma cell emboli and cases considered by the pathologist to be true pulmonary artery thrombosis. In order to eliminate errors in coding and cross-referencing, each autopsy record was individually reviewed.

Comment has already been made in a prior paper in this series (7) regarding the deliberate selection of a large consecutive autopsy series in order to secure maximal diagnostic accuracy; it was demonstrated that clinical diagnosis of thromboembolism is so grossly inadequate that no clinical series would be of value in obtaining valid information concerning the true incidence of this disease or the influence of epidemiologic factors.

Statistical methods were those outlined by Snedecor. Any values for p of greater than .05 were not considered significant.

Since any tentative conclusions drawn from a study such as this depend upon a statistical approach, several comments should be made concerning the accuracy of these techniques. Naturally the series must be big enough so that the many subcategories are of sufficient size to permit valid statistical analysis. In addition, one must obtain a group for study which includes as much as possible a group representative of a segment, at least, of the hospital population. In the choice of a series of consecutive complete autopsies there is automatically some selection: (1) that portion of the hospital population that was seriously ill, and for the most part, confined to bed; (2) that portion of hospital fatalities in which permission for autopsy was granted. In addition, there is inevitable variability in the accuracy of autopsy and clinical records which, it is hoped, the size of the series will equate in part. Furthermore, in the evaluation of numerous diagnostic, pathologic, and epidemiologic factors, one must assess the influence of each factor with the realization that one or more other variables may have an appreciable influence on the statistical data obtained. For example, in examining the true incidence of pulmonary embolism in patients with carcinoma or heart disease, one must be certain that any increased incidence of pulmonary embolism is not due to differences in age alone, since, as we shall show, age plays a critical role in influencing the incidence of pulmonary embolism in any category. These comments have been presented to point out a few of the many objections frequently raised in any statistical study of multiple factors in human beings; that these variables exist is inevitable. One cannot ignore them in critically assessing the results of this and other human studies; however, at the same time, because of human individuality, one cannot eliminate them from a study of this sort. It should be emphasized that any conclusions derived should be considered tentative and approximate rather than definitive.

RESULTS

Total incidence. During the 10 year period from 1945 through 1954, there were 4,391 complete autopsies; in 606 of this group pulmonary arterial emboli were found, an over-all incidence of 13.8 per cent.

Age and sex incidence. Figure 1 demonstrates the almost linear increase in absolute incidence of pulmonary embolism when this incidence is plotted by 10 year age groups. These figures are absolute in that incidence has been obtained by dividing the number of patients with pulmonary embolism in particular age groups by the total number of patients in the entire autopsy population who fall into that age category. The slight peak in the 10 to 19 year age group is thought to be due to the higher incidence of pulmonary embolism in association with the greater frequency of death due to physical trauma in males at this age. There is a higher than expected incidence of pulmonary embolism in males in the 15 to 20 year age category only. When larger than 10 year age divisions are used, the relationship between pulmonary embolism and advancing age shows a more truly linear increase.

It is interesting that of all those patients coming to autopsy between the ages of 0 to 9 years, 1 in 35 had pulmonary embolism; between the ages of 10 and 34, 1 patient in 12 had a pulmonary embolus; between 35 and 54, 1 in 7; between 55 and 74, 1 patient in 5; and of all patients aged 75 years and over, 1 in 4 had an embolus in the pulmonary arterial tree at necropsy.

There was no significant difference in sex

distribution or age-sex distribution of pulmonary emboli when the incidence was computed on an absolute basis. There were 397 male patients with emboli as compared to 209 females; however, when one calculates incidence on the basis of the entire autopsy group, it is almost identical, since in the group as a whole, males also outnumber females almost 2 to 1. The increased number of pulmonary emboli seen in the 15 to19 and, to a lesser extent, the 20 to 24 year ages in males was notable, but there were too few cases of embolism in these categories for the differences to be statistically valid.

Seasonal incidence and annual incidence. Seasons are difficult to define in Michigan, but since DeTakats and associates have suggested a seasonal increase in incidence of this process, the quarterly distribution of pulmonary embolism was assessed by dividing the year into four 3 month quarters. There was no valid difference in incidence of pulmonary embolism in different quarters of the year.

There was a significant difference in annual incidence of pulmonary embolism (evaluated by the Brandt and Snedecor method for enumeration data with multiple degrees of freedom; p= less than .025). Interesting also was the fact that there was a significant decrease in incidence of pulmonary embolism during the latter 5 years of the study when compared with the first 5 years (p = less than .05).

Many authors have commented on the marked variations in frequency of pulmonary emboli over an extended period of time. This observation was also made in this series in which, when incidence was plotted by 3 month quarters, pulmonary embolism varied in frequency from 4 to 23 per cent of all autopsies within those quarterly periods. However, valid differences not expected on the basis of random variation alone were observed only in annual incidence as mentioned before.

Incidence by service. The distribution of pulmonary embolism by service did not differ significantly from that observed for the entire autopsy population (13.8 per cent pulmonary embolism rate) except on the general surgery (24.8 per cent), gynecology (32.0 per cent), and urology services (21.6 per cent). When these results were evaluated on the basis of age-expected incidence for the age distributed autopsy population on these services, it was found that increased incidence of pulmonary embolism on the urology service might have been due to the higher percentage of patients of advanced age. However, the increased number of pulmonary emboli on the general surgery and gynecology services could not be explained on the basis of age alone.

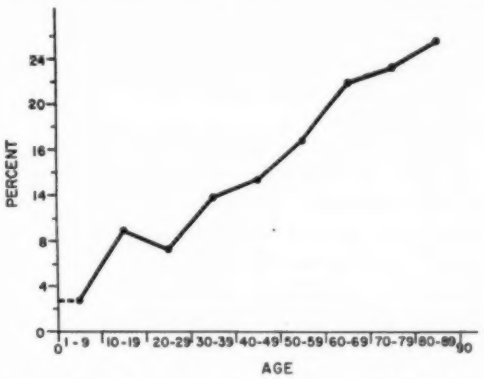

FIG. 1. Absolute incidence of pulmonary embolism by 10 year age groups in 4,391 autopsies at the University of Michigan Hospital.

The incidence of pulmonary embolism in patients from the pediatric service (2.8 per cent) equated very well with age expected incidence for that group.

Influence of heart disease. In the entire autopsy series of 4,391 patients, 1,346 had pathologically demonstrable heart disease; any patient in whom the prosector listed evidence of heart disease was included, regardless of whether this was an incidental finding or of serious import to the patient. There were 332 or 24.7 per cent of those patients with heart disease who had demonstrable pulmonary emboli. Of the remaining 3,045 autopsied patients who had no heart disease, regardless of other pathologic conditions, the over-all incidence of pul-

monary embolism was 9.0 per cent. This greatly increased incidence of pulmonary embolism in association with heart disease is highly significant statistically (p= less than .001).

When the heart disease was subdivided by type, there was no significant difference in the incidence of pulmonary embolism from one type of heart disease to another other than the very low incidence one might expect in congenital heart disease on the basis of age alone. It is interesting that the highest incidence of pulmonary embolism was seen in rheumatic heart disease (32.1 per cent) in spite of the fact that these patients had a peak age distribution 15 to 20 years younger than those with degenerative heart disease (pulmonary embolism rate=25.8 per cent). On the basis of age alone, one would expect to see a higher incidence in the latter group. One must assume, therefore, that other factors operate to elevate the incidence of pulmonary embolism in these younger patients; the explanation might be provided by the higher incidence in this series of congestive heart failure in patients with rheumatic heart disease as compared to those with degenerative heart disease.

It was surprising to find that patients with bacterial endocarditis had no higher incidence of proved pulmonary embolism than the group as a whole.

Likewise, it was expected that patients with pathologically demonstrated acute or old myocardial infarcts (606 patients) would have a higher pulmonary embolism rate. However, the difference in pulmonary embolic rate observed between those patients with myocardial infarcts (27.2 per cent) as compared with those without this lesion (22.6 per cent) was not statistically significant (p = less than 0.1 but greater than .05). The difference was no greater when patients with acute myocardial infarcts were considered separately.

Auricular fibrillation was associated with a very high incidence of pulmonary embolism. Of the 131 patients in the entire autopsy series with auricular fibrillation, 75 or 57.3 per cent had pulmonary emboli. In only 17 of this group with auricular fibrillation and pulmonary embolism were right mural thrombi demonstrated at autopsy. This discrepancy could be explained by the fact that: (1) in the other cases a fresh right mural thrombus was completely dislodged, producing pulmonary embolism without leaving evidence of thrombotic involvement of the right heart or, (2) the auricular fibrillation was incidental, merely indicative of advanced heart disease which is always associated with a higher frequency of pulmonary embolism, and the pulmonary embolus originated in a leg vein source.

After a careful review of the problem of congestive heart failure, it was concluded that the approach utilized in this study would not provide valid statistics concerning the true frequency of pulmonary embolism in association with heart failure. The difficulties in pathologic diagnosis of congestive heart failure and the intricacies of the clinical coding system then in effect would have necessitated complete and careful review of clinical records in all 1,346 patients to obtain valid figures concerning the true incidence of this entity. For this reason, no absolute figure will be presented with regard to the role of congestive heart failure as a factor predisposing to the development of pulmonary embolism. An evaluation of autopsy data alone suggests that heart failure of the congestive type was present with much greater frequency in patients with pulmonary embolism as compared to those without pulmonary emboli, but we do not believe that this approach is entirely valid as far as determining absolute incidence of pulmonary embolism in congestive heart failure is concerned.

As might be expected, 62.2 per cent of patients with right mural thrombi had pulmonary emboli, a threefold increase in frequency over that seen in the remaining patients with heart disease. There was a further increased incidence of pulmonary embolism in patients who had congestive heart failure

in association with the right mural thrombosis as contrasted to those with right mural thrombosis but without congestive failure. This difference was statistically valid.

If one assumes that some pulmonary emboli are derived from a cardiac source, then one must know the incidence of right mural thrombosis in patients who have pulmonary emboli as compared to the incidence of right mural thrombosis in patients without pulmonary embolism. The incidence rate was 16.9 per cent for the former group as compared to 3.4 per cent for the latter. This fact suggests that right mural thrombi are 5 times more frequent in patients with pulmonary emboli (and heart disease) as contrasted to those with heart disease but without pulmonary embolism. If the further assumption is made that in all patients with both right mural thrombosis and pulmonary embolism the embolus originated from the cardiac source (rather than the leg veins), then a maximum of 4 of every 5 right mural thrombi ultimately result in pulmonary embolism.

As far as this series is concerned 56 of 90 patients with proved right mural thrombi were found to have pulmonary emboli. Even assuming that in all 56 of these patients with pulmonary emboli the embolus arose from this locus in the heart, then a maximum of 9.2 per cent of the 606 patients had pulmonary emboli which were definitely proved to have originated from a cardiac source. This assumption ignores the fact that, in spite of the presence of a right mural thrombus, the embolus may well have come from the leg veins. This figure of 9.2 per cent seems to be reasonable and perhaps approximately correct if one equates this possibility with the likelihood, mentioned previously, that some of the patients with auricular fibrillation had emboli secondary to a right mural thrombus which had become completely dislodged and left no evidence at autopsy. This reasoning is presented to emphasize that the great preponderance of emboli arise from a leg vein source.

TABLE I.—INCIDENCE OF PULMONARY EMBOLISM IN 1,394 CANCER PATIENTS

	No. of patients	*Incidence*	
		No.	*Per cent*
Group I: High incidence of pulmonary embolism			
Male and female genitourinary cancer	221	61	27.6
Cancer of the lung	157	29	18.5
Gastrointestinal tract cancer (including biliary tract and pancreas)	407	95	23.3
Thyroid carcinoma	13	6	—
Total	798	191	23.9
Group II: Low incidence of pulmonary embolism			
Lymphomas (leukemia, etc.)	363	31	8.5
Breast cancer	52	5	—
Malignant lesions in central nervous system	77	5	—
Oral, pharyngeal, and upper respiratory tract cancer	32	5	—
Other malignant lesions	72	8	—
Total	596	54	9.1

Influence of cancer. All malignant neoplasms occurring in the 4,391 patients were tabulated as to type and location. There is considerable controversy as to what constitutes a malignant neoplasm of the central nervous system; obviously benign lesions and slow-growing lesions (ependymoma, spongioblastoma, low-grade astrocytomas) which were malignant only because of location were omitted.

There were 1,394 patients with malignant conditions satisfying these criteria. Of this group 17.1 per cent had pulmonary embolism. Forty-four patients had coexisting multiple malignant neoplasms, and, of these, 11 had pulmonary emboli. These figures may be contrasted with an incidence of pulmonary embolism in patients without malignant tumors (regardless of other disease) of 12.3 per cent. None of these differences, however, are statistically valid. The reasons for this lack of significant difference will be explained subsequently.

In the breakdown of neoplastic disease by location, there was a considerable variation in the incidence of pulmonary embolism. As Table I shows, there was 1 group of patients with a high incidence of emboli

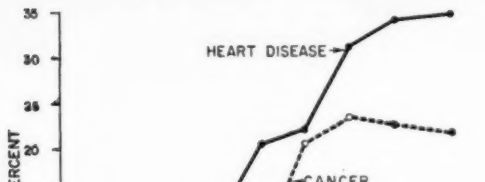

FIG. 2. Absolute incidence of pulmonary embolism by 10 year age groups in all patients with (1) heart disease (but no cancer), (2) cancer (but no heart disease), and (3) neither heart disease nor cancer.

while the rest of the group had an incidence similar to that seen in a noncardiac, noncancerous population.

The highest incidence of pulmonary embolism was seen in patients with carcinoma of the pancreas and carcinoma of the prostate gland. Fifteen of 44 patients (or 34.1 per cent) with carcinoma of the pancreas and 26 of 70 (or 37.1 per cent) with carcinoma of the prostate had pulmonary emboli. These groups are so small, however, that neither percentage incidence is significantly greater than that seen in the remaining patients in group I.

Similarly, when one calculates age-expected incidence of pulmonary embolism for each of the subgroups of patients with cancer having a high incidence of pulmonary embolism, only patients with genitourinary neoplasms have a significantly increased incidence of embolism over that expected on the basis of age alone. However, this failure to demonstrate a significant variance from age-expected incidence may be due to the small size of these groups; much larger individual groups may tend to accentuate differences not seen in small series. It is perhaps for this reason, plus the marked difference in embolism rate seen in genitourinary cancer, that the incidence of pulmonary embolism in group I does show a significant difference from the age-expected incidence.

Interrelationship of age, cancer, and heart disease. In an attempt to study the influence of heart disease and cancer and a combination of both on the incidence of thromboembolism, these figures were obtained:

The incidence of pulmonary embolism in 1,910 patients with neither cancer nor heart disease was 6.0 per cent; in 1,135 patients with cancer but without heart disease, 14.1 per cent; in 1,087 patients with heart disease but without cancer, 22.6 per cent; in 259 patients having both heart disease and cancer, 33.2 per cent. (Each value is significantly different from each of the others.)

This suggested that both cancer and heart disease were factors predisposing to pulmonary embolic complications and that a combination of both factors present in the same patient had a cumulative effect in a further increase in incidence of pulmonary embolism.

To assess the role played by age in this pattern, the age incidence of pulmonary embolism was plotted for each of the first three groups (Fig. 2). Values for age incidence were not included in the cancer and heart disease categories for age groups below the age of 30 years because the number of pulmonary emboli were too small to give significant figures. This graph shows very little increase in incidence of pulmonary embolism with advancing age in patients who did not have either cancer or heart disease; it suggests that the increasing incidence of pulmonary embolism with advancing age is related less to the primary influence of age per se than to the combined influence of heart disease or cancer and increasing age. Further suggestive evidence that cancer and heart disease play a real role in producing an increase in incidence of pulmonary embolism is provided by Figure 3 which shows an almost linear correlation between the increased incidence of cancer and heart disease with advancing age and the similar increase in incidence of pulmonary embolism.

Influence of obesity. All patients were considered obese whose weight was greater than 10 per cent over the maximum "ideal" weight for large frame individuals of graded height. These figures were obtained from life insurance tables. Weights 10 per cent greater than ideal maximums for large frame patients are equivalent to a 20 per cent increase over standard weights for 30 to 34 year age groups as listed in the usual life insurance standard weight tables. These figures were considered to represent true obesity; for example, minimum weight for a 5 foot 9 inch male, to be considered obese by these criteria, was 187 pounds; for a 5 foot 3 inch female, 152 pounds.

Patients were then further subdivided into groups of: less than 20 per cent over maximum ideal weight, 20 to 29 per cent, 30 to 39 per cent, and 40 per cent or greater increase over maximum ideal weight. All patients under 20 years of age were omitted as were a few patients with amputations or no recorded weight.

No difference in incidence of pulmonary embolism was found between obese and nonobese males. However, the incidence of pulmonary embolism in obese females (22.5 per cent) was significantly higher than that in nonobese females (13.3 per cent); p = less than .01. This surprising difference may be explained on the basis of the fact that extreme obesity (30 per cent or more over maximum ideal weight) was seen much more frequently in females with pulmonary embolism than in the rest of the feminine autopsy population. The trend to extreme obesity was seen much less often in the male population. It was in the groups with the greatest obesity that the highest incidence of pulmonary embolism was found, but, because of the small size of each subgroup, the variation in incidence between subgroups could not be proved to differ significantly. The incidence of pulmonary embolism in all patients (male and female) 30 per cent or more overweight by these standards did differ significantly from the incidence seen in all remaining patients (p = less than .005).

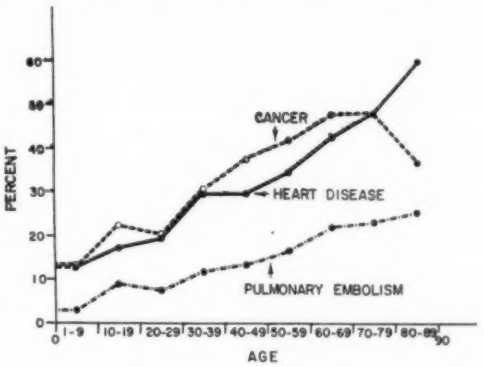

FIG. 3. Absolute incidence of heart disease, cancer, and pulmonary embolism by 10 year age groups in 4,391 autopsies.

Influence of tuberculosis. Comment has been made in the literature that tuberculosis is associated with a very low incidence of thromboembolic disease. In this autopsy series, 156 patients had active tuberculosis and 14 of this group had pulmonary emboli. There was no significant difference in incidence of pulmonary embolism in those patients with tuberculosis as compared to the remainder of the autopsy population. This is also true when only those patients with pulmonary tuberculosis are considered (10 of 60 had pulmonary emboli).

Influence of operation. It has not been possible, in a necropsy survey of this sort, to obtain statistics of sufficient validity concerning the true influence of operative trauma on the incidence of pulmonary embolism. As prior portions of this study have shown, multiple other interrelated variables make the accurate evaluation of many single factors difficult if not impossible. Gross figures, without adjustment, indicate a twofold increase in incidence of pulmonary embolism in surgical as compared to nonsurgical patients in this series; however, when one considers adjusting the expected incidence for the increased number of cancer patients in the group operated upon and the older age distribution of postoperative deaths, the difference in pulmonary embolic incidence becomes negligible. The problem

then centers around the perennial question of which factor is primary and which is of secondary importance. The same considerations relate to our difficulties in attempting a breakdown of embolic incidence according to specific types of operations. One could eliminate some of these variables by considering patients in a specific age group with a specific neoplasm who did or did not have a specific operation; in a series of this size, however, such an approach is not feasible.

The relationship in time between operation and occurrence of the first pulmonary embolus elucidates one interesting facet of this problem. Gibbs has recently presented some data to suggest that the greater the period of immobility, the greater the incidence of venous thrombosis. Certainly, the vast majority of patients submitted to operation are immobilized to a considerably greater extent in the postoperative period than they were preoperatively. Figure 4 graphically presents the time relationship between operation and pulmonary embolus in 205 patients who had emboli in the postoperative period and in whom there were clinical manifestations which seem to indicate the time at which pulmonary embolism occurred; there were another 52 patients in whom the time of embolus could not be determined or in whom the embolus occurred more than 28 days postoperatively. It was somewhat surprising to us to find that the highest incidence of postoperative pulmonary embolism was within the first 24 hours postoperatively, rapidly decreasing in incidence after the first 2 postoperative days. Twenty-six per cent of known postoperative emboli occurred within the first 2 days, a cumulative 52 per cent within the first week, and 72 per cent within 2 weeks after operation. These figures suggest at least that many venous thrombi may occur upon the operating table.

In addition to 257 postoperative emboli cited, there were another 12 patients in this series who had pulmonary emboli following ligation of the superficial or common femoral veins or the vena cava.

Other factors possibly influencing the incidence of thromboembolic disease. There are a number of other factors which may play a role in predisposing to the development of thromboembolic disease. Gibbs has shown that the degree of immobility is of real importance; corollary to this, Byrne has remarked on the apparent high frequency of thromboembolic disease in patients with paralysis. It would not have been possible to evaluate either factor adequately in this series without a careful review of clinical records in all 4,391 patients; paralysis and paresis are linked (but not always associated) with so many disease entities that only individual review of the records could have provided accurate data. We also were impressed with the apparently high frequency of paralysis and paresis in this group of patients with pulmonary emboli.

A similar approach would have been necessary to evaluate properly the incidence of pulmonary emboli in patients with a prior history of deep venous thrombosis, a factor which we think is of extreme importance.

Initially, an attempt was made to assess the influence of leg vein trauma, but this was found to be impracticable since, in many of the patients in whom we thought that leg trauma played a role, the source of the trauma was related to such nonspecific procedures as cut-downs or simple needle administration of fluids in leg veins and insertion of Kirschner wires through the lower end of the tibia for traction. The incidence of pulmonary embolism in association with ulcerative colitis appeared to be much higher than one would expect in a young, noncancer group of patients. Seven of 27 patients (26 per cent) had pulmonary emboli. This number of patients is too small to be statistically significant. Certain other disease states which have been incriminated as of possible epidemiologic significance in pulmonary embolism (e.g., collagen disease, hematologic diseases other than leukemia, especially polycythemia rubra vera) were not present in sufficient quantity to allow for adequate statistical evaluation.

DISCUSSION

This study has attempted to provide valid statistical data concerning the role played by certain possible epidemiologic factors in influencing the incidence of pulmonary embolism. The goals and criticisms in the use of a statistical approach have been discussed previously. It should be re-emphasized that the complexity of the statistical approach in the face of multiple variables must make the conclusions that have been drawn tentative rather than definitive. However, we believe that the technique used for determining absolute incidence of pulmonary embolism in certain age groups and disease states in a large well examined autopsy population provides more valid information concerning epidemiologic factors than much of the previously published data.

As the previous paper in this series has demonstrated (7), any statistics based on purely clinical diagnosis of pulmonary embolism will be grossly inaccurate, presenting inordinately low figures for true incidence; in this series a definitive clinical diagnosis of pulmonary embolism was made either before or after death in only 12.9 per cent of the total cases proved at autopsy. DeBakey has remarked on the great variability in incidence of pulmonary embolism reported in autopsy series from various parts of the world. This variability may be due to a number of factors: (1) the age distribution and types of disease causing death in the autopsy population from a particular hospital, (2) the type of autopsy performed (? routine sections of various areas of lung), (3) the alertness of the individual prosector to the possibility of fatal pulmonary embolism, with particular reference to microscopic study of questionable antemortem thrombi in the pulmonary arterial tree.

The variation in annual incidence of pulmonary embolism which was noted in this series has also been described by other investigators. These considerable fluctuations in incidence are difficult to explain; some of the factors noted before may be responsible. It is interesting that in spite of annual variations in incidence, no significant seasonal variations were found. Both McCartney and Pilcher arrived at similar conclusions from their autopsy studies. It is difficult to conceive that meteorologic fluctuations associated with the changing seasons would have any influence on pulmonary embolism, and there is no good evidence to support this postulate.

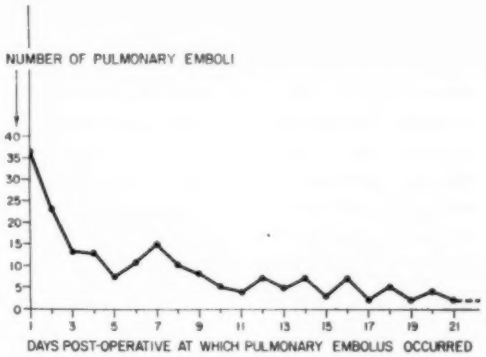

FIG. 4. Time relationship between operation and pulmonary embolus in patients who had pulmonary emboli in the postoperative period.

Sex does not have a demonstrable influence on the epidemiology of pulmonary embolism. Age, as our graphs show, has a very profound effect on the frequency of this complication. McCartney and Hillemanns found a similar progressive increase in absolute incidence of pulmonary embolism with age. However, our compiled data on cancer and heart disease suggest that pulmonary embolism increased in frequency with advancing age primarily in those patients who had heart disease or cancer; the predominant influence of age, then, seems to be a combined one, showing its greatest influence when heart disease or cancer is also present.

It is always interesting to speculate on the epidemiologic significance of the increased incidence of pulmonary embolism referable to particular hospital services. As far as this series is concerned, determination of absolute incidence by service revealed a discrepancy, not explainable on the basis of age alone, only on the general surgery and gynecology services. An explanation derived from

our other data would relate this increased incidence to a distribution on these services of more patients having neoplasms known to be associated with a higher incidence of pulmonary embolism. Ochsner and associates have reported a similar increase in incidence of fatal pulmonary embolism on the gynecology service alone; they explain this higher incidence on the basis of a large number of patients with puerperal sepsis on that service. Puerperal sepsis or pelvic inflammatory disease from other causes with its associated high incidence of true septic thrombophlebitis is very rare at our hospital. It is logical to assume that an increased incidence of pulmonary embolism on a particular service may be quite variable from one institution to another, since the frequency of this complication is determined in great measure by the types of patients seen in that hospital. As our figures demonstrate, our hospital differs from others in the very high proportion of patients with chronic disease, particularly cancer, as contrasted to hospitals in large cities where deaths from trauma and acute nonneoplastic disease are seen much more frequently.

Heart disease, even well compensated heart disease, is of critical importance in influencing the incidence of pulmonary embolism. If one contrasts the incidence of pulmonary embolism in a basal population of patients without heart disease or cancer with the entire group of patients having heart disease (but without cancer), the frequency of pulmonary embolism is 3½ times as great. McCartney and Moran have reported almost identical figures with reference to the effect of heart disease on pulmonary embolic incidence. If one selects patients with more severe heart disease as characterized by the presence of auricular fibrillation, the incidence of pulmonary embolism is almost 10 times that of the "basal group." Rosenthal, White and others (6, 24) have demonstrated a similar high incidence of thromboembolic disease in association with cardiac decompensation as well. White (24) found that 48 per cent of cardiacs with congestive heart failure who died had pulmonary embolism proved at autopsy. Our tentative figures would suggest an equally high value for this series of cases, but, because of technical difficulties in the diagnosis of congestive heart failure from autopsy findings alone, we are reluctant to list a definite percentage figure.

It was expected that patients with myocardial infarction would show a higher incidence of pulmonary embolism. Although embolic incidence in this group was not significantly greater than that for the remaining patients, the probability value was less than 0.1; it is quite likely that a larger series might have accentuated this difference so that a proper degree of significance would have been reached.

The finding that right mural thrombi are 5 times as common (on an absolute incidence basis) in cardiac patients with pulmonary emboli as contrasted to cardiac patients without pulmonary embolic complications suggests that right mural thrombi are a source of potential pulmonary embolism. Even assuming that all pulmonary emboli occurring in patients in this series with right mural thrombi originated from the heart, then a maximum of 9.2 per cent of all pulmonary emboli could have been derived from a cardiac source. If one accepts the steps in arriving at this rough estimate, then the cardiac origin of pulmonary embolism is a minor factor in the over-all consideration of the sources of pulmonary emboli. This argument has been presented to emphasize what we believe is the predominant role of leg vein thrombosis as a source of pulmonary emboli, even in cardiac patients. In cardiac patients alone our data suggest that over four-fifths of all emboli come from leg or pelvic vein sources. White and his colleagues (6) have arrived at similar conclusions.

Unfortunately, the excellent studies of deep venous thrombosis based on complete leg vein dissections have not included information on the incidence of cardiac right mural thrombi, or, more important, a comparison of demonstrable leg and cardiac thrombi in patients with heart disease as a

source of actual or potential pulmonary emboli. Consideration of our figures in conjunction with those of McLachlin and Paterson and Gibbs has allowed us to make some very gross assumptions with regard to the most proximal location of the thrombus in cases of thromboembolic disease: (1) less than 10 per cent of all pulmonary emboli originate from a cardiac source; (2) less than 3 per cent of patients have caval involvement; (3) another 10 per cent have demonstrable involvement of major pelvic veins; (4) the sources for the remaining three-fourths of all pulmonary emboli originating in the leg veins have varied considerably in various series; debate has centered more about the initial origin of the thrombus, however, rather than its proximal extent. It is our belief that only about half of the thrombi in leg veins are confined to the superficial femoral vein and its tributaries while the other half involve profunda femoris or common femoral vein sites where bilateral superficial femoral vein ligation would not prevent subsequent emboli. McLachlin and Paterson have demonstrated in their series of leg vein dissections this fallacy in the utilization of superficial femoral vein ligation as a measure to prevent pulmonary embolism.

This study has shown that there is a statistically significant difference in incidence of pulmonary embolism between a "high risk" group of patients with certain types of cancer and the remaining patients with malignant neoplasms. There is no immediately evident common factor associated with the high risk group of patients which one can point out as of etiologic significance. A large proportion of the high risk group had adenocarcinomas, but bronchogenic carcinoma and carcinoma of the cervix are notable and major exceptions to this generalization. A slightly greater proportion of this group had operations, and the trauma of operation may have played some role in affecting embolic incidence. However, almost all of our patients with cervix lesions were treated by irradiation alone, and the majority of cases of carcinoma of the lung were inoperable. Similarly, more than half of the patients with prostatic carcinomas had no operation, and about one-third of those with gastrointestinal carcinomas had no operative procedure during their final hospital admission. Although operation may play a role in this difference in incidence of pulmonary embolism, it does not seem to be the only factor.

Lesions and operations in the true pelvis have been incriminated by other investigators as significant epidemiologic factors in pulmonary embolism; this association has usually been explained on the basis of the close proximity of these lesions and procedures to the pelvic veins.

The name of Trousseau has been linked with the syndrome of thromboembolic disease in association with cancer, particularly carcinoma of the pancreas, although Trousseau's original descriptions were with reference to carcinoma of the stomach. The incidence of pulmonary embolism in patients with carcinoma of the pancreas was high in this series, but it was not significantly higher than in other gastrointestinal cancers; this may be related in part to some recent suggestive evidence that thromboembolic disease is extremely common only in carcinomas of the body and tail of the pancreas. There were insufficient numbers of lesions of this type to confirm this impression.

Patients with the high risk group of neoplasms had a two to fourfold increase in the incidence of pulmonary embolism over that seen in the low risk group of cancer patients. Even when the entire cancer group (exclusive of those cancer patients with associated heart disease) is compared with the basal group of patients without cancer or heart disease, there is greater than a twofold increase in incidence of pulmonary embolism.

Attempts to interrelate cancer, heart disease, and age led to some interesting findings. To see whether these epidemiologic influences were cumulative, the incidence of pulmonary embolism was determined in patients having both heart disease and cancer and found to be higher than with

either pathologic lesion alone and about 5½ times the incidence in the basal group of patients without either lesion. The differences between each of these groups were highly significant. This observation is suggestive evidence that the epidemiologic influences of these factors, when more than one factor is present in the same patient, may be additive. In addition, age correlation of cancer, heart disease, and pulmonary embolism, as demonstrated in Figures 2 and 3, shows that although age alone plays a minor role in influencing pulmonary embolic incidence in patients without heart disease or cancer, age is of far greater significance when one or both of these pathologic lesions are present. In patients 40 years of age and older with heart disease and patients with cancer, aged 50 years and older, there is a sharp rise in incidence of pulmonary embolism. Age is a critical secondary factor in these two diseases since absolute incidence of pulmonary embolism in each 10 year category in each disease rises in the age categories specified before. The rise in age incidence of pulmonary embolism in absence of these two disease entities (basal group) is minimal.

The relationship of obesity to an increased incidence of pulmonary embolism was noted by Snell more than 30 years ago; he also observed that the degree of obesity was influential in affecting embolic rate. The finding in this study of a significant increase in embolic incidence (twofold) only in obese females seems to be related to the size of the series and the increased frequency of extreme obesity in women rather than to any selective influence of obesity in one sex. Barker and associates (3), reporting a post-hysterectomy series, have demonstrated a twofold increase in pulmonary embolism in women weighing more than 200 pounds. If a larger number of obese males were evaluated, especially those more than 30 per cent over ideal weight, it seems likely that a similar valid increase in pulmonary emboli would be seen in men as well; neither Hillemanns nor Snell reported any sex differences in the effects of obesity.

This study has presented data to suggest that, as far as autopsy correlation is concerned, pulmonary embolism is as common in patients with tuberculosis as in the remaining autopsy population. It would be illogical to postulate any unique protective influence of tuberculosis in lowering the incidence of pulmonary embolism. Patients who die with tuberculosis are less likely to have heart disease or cancer, factors which are associated with a higher pulmonary embolic rate. Clinical studies of large groups of patients with tuberculosis have been reported to show a very low incidence of pulmonary embolism. Such a finding is not unexpected and, in our opinion, should not be used to refute the importance of immobility as an epidemiologic factor in pulmonary embolism. Tuberculous patients are, for the most part, an otherwise healthy group whose restriction to bed does not constitute the kind or degree of immobility one sees in seriously ill patients with heart disease, cancer, or hip fractures. Jones, Black, and Sparr have reported from a tuberculosis hospital that in 60 consecutive autopsies in which careful dissection of the pulmonary arterial tree was carried out, there were 11 instances of pulmonary embolism. This is almost identical with the incidence observed in the 60 patients with pulmonary tuberculosis in this series (10 of 60 with pulmonary embolism).

The difficulties in evaluating the role of operation in pulmonary embolism have been discussed. It may well be that the apparent twofold increase in incidence of pulmonary embolism in postoperative patients is secondary to one of many other existing variables. Barker and his colleagues (2) have reported an increased incidence of postoperative pulmonary embolism after abdominal operations, especially those involving organ resection. There is little question that this is a valid observation, but this increase in incidence may be associated with a higher percentage of cancer patients in this group rather than to the influence of operation per se. Similarly, the observation that pulmonary embolism occurred 3 times

as frequently after operation for a ruptured appendix as compared to uncomplicated appendectomy could be explained on the basis of the more prolonged immobility associated with a ruptured appendix, whether an operation is performed or not. The observations of Gibbs suggest that the influence of operation upon pulmonary embolism may be related in many instances more to the increased immobility of the patient created by the operative procedure than to any specific alteration in coagulation mechanism directly attributable to operation.

If such an assumption is true, then the proponents of early ambulation have a valid argument for the value of this regimen as one prophylactic measure useful in lowering the incidence of thromboembolic disease. However, for this specific purpose, early ambulation, as usually practiced, is both impractical and useless. Allowing a patient to sit up in a chair or to walk for 5 minutes several times a day and then placing him back in bed for 23 hours and 45 minutes would seem to be of little value in the prolonged and sustained augmentation of venous return necessary for successful elimination of the stasis factor which may be of etiologic significance in thromboembolic disease. The patient who has had a major intra-abdominal operation is frequently incapable of much more vigorous ambulation than this. The observation by Paulsen and associates that both mild elevation of the legs and elastic bandage wrapping of the legs lead to a significant increase in venous blood flow from foot to groin suggests a much more practical measure, easily performed, which may have prophylactic value. It is a simple procedure to have every patient's legs wrapped with elastic bandages prior to operation; elastic bandage wrapping and slight elevation of the legs should be maintained until the patient is fully ambulatory.

It was somewhat surprising to us that, in this series at least, the highest incidence of postoperative pulmonary embolism was within the first 24 hours after operation. If one assumes on this basis that total immobility under anesthesia may play an occasionally significant role in venous stasis, deep venous thrombosis, and subsequent pulmonary embolism, then further studies are necessary to attempt to find a simple and effective means for increasing rate of venous return during the operative procedure and the period of postanesthetic recovery. Wrapping and elevating the legs on the operating table is a simple approach which is now available. Mechanical devices for intermittent compression of the calf or continuing motion of the toes or feet are now under investigation.

The best data available on the extreme importance of a prior history of deep venous thrombosis in the prediction of the high likelihood of subsequent pulmonary embolic complications are those of Barker and his associates (3). Forty-six patients, all with a prior history of deep venous thrombosis, underwent hysterectomy. Thirty-one had postoperative pulmonary emboli and 15 of these died from fatal pulmonary embolism. All of our patients who have a prior history of deep venous thrombosis, regardless of time interval, are placed on prophylactic anticoagulants in the early postoperative period unless a major contraindication to anticoagulants exists.

The relationship between leg trauma and thromboembolic disease is well known. Bauer has reported an eightfold increase in thromboembolism following trauma to the legs. The incidence was especially high in extensive soft tissue injuries and in fractures of the major bones of the legs. Aubigne and associates have reported that 15 per cent of orthopedic service mortality in their hospital has been due to fatal pulmonary embolism. The highest incidence was subsequent to operations upon the hip. They also comment on the ominous prognostic significance of a prior history of deep venous thrombosis. Mills has made some interesting observations on the hazards of Kirschner wire traction through the lower end of the tibia; correct placement of Kirschner wires through

the lower end of the tibia in cadavers frequently resulted in compression or laceration of the anterior tibial vein. We have become impressed that another iatrogenic source of pulmonary embolism is the very high incidence of deep venous thrombosis following either needle or polyethylene catheter administration of fluids in leg veins. We feel very strongly that all other practical sources for parenteral fluid administration be utilized before deliberate leg vein trauma is produced by such procedures.

What do the findings of this study contribute to our knowledge concerning the primary etiology of venous thrombosis? They tend to substantiate the original postulates which Virchow established more than 100 years ago. The decrease in venous return accompanying immobility from serious illness, obesity, and heart failure seems to be a major factor. However, it is well known that by experimental, relatively atraumatic isolation of a segment of vein one may retain fluidity of blood within the vein for a considerable period of time. So, this stasis factor involves more than a momentary decrease in venous blood flow; one can hope that with the previously suggested simple methods of leg wrapping and of elevation one might be able to alter in part this factor of possible etiologic significance in venous thrombosis. It has also been well established that trauma to a vein wall is the simplest and most effective method of inducing venous thrombosis in experimental animals. The lessening of leg and pelvic vein trauma can only be accomplished by very careful attention to operative technique and by realization of the hazards accompanying administration of any agents by way of the superficial veins of the leg. The third factor postulated by Virchow, alteration in the coagulability of the blood, may be the primary element in the etiology of thromboembolism. However, this and many other laboratories have been searching for a number of years to attempt to demonstrate that an alteration in one or more of the circulating clotting factors is uniformly present prior to the onset of spontaneous intravascular thrombosis. The difficulties in establishing objective proof for such a postulate are self-evident. The major problem in such investigations in humans is our inability to establish accurately who does and does not develop venous thrombosis because there are no clinical signs or symptoms in the great majority of cases. Animal studies are not applicable since the manipulations necessary to produce venous thrombosis in animals automatically invalidate any conclusions which might be derived from such a study.

At our present state of knowledge, granting our very poor diagnostic accuracy and the paucity of fundamental information concerning the primary etiology of spontaneous venous thrombosis, the only rational approach which may prove of value in the salvage of patients who will otherwise die from fatal pulmonary embolism is a program of effective prophylaxis in a selected group of patients with a high predisposition to the development of thromboembolic disease. Some data concerning the efficacy of anticoagulant therapy in the prevention of fatal pulmonary embolism have been presented in a prior paper from this laboratory (8). Other groups have reported large series demonstrating the value of anticoagulants as truly prophylactic agents in significantly lowering the incidence of thromboembolic complications. The major objection raised to a program of mass prophylaxis is the time, money, and energy expenditure necessary to carry out such a program in an entire hospital population. One of the purposes of this study has been to provide epidemiologic data which might be utilized to calculate the relative risk of pulmonary embolism in any individual patient with one or more of those epidemiologic factors thought to play a role in increasing the incidence of thromboembolic disease. On this basis the clinician has some rational means for selecting those patients who might obtain greater benefit from prophylactic anti-

coagulant therapy. We still believe that pulmonary embolism should be a preventable disease. Prophylactic anticoagulant therapy is a rational method for saving most of those patients now dying from this complication.

SUMMARY

Data derived from a large consecutive autopsy series have been utilized to demonstrate the role of some epidemiologic factors in influencing the incidence of pulmonary embolism. Heart disease, cancer, and advancing age have been shown to have a predominant and interrelated effect on the absolute incidence of this disease. On the basis of this epidemiologic information, a program of prophylactic anticoagulant therapy in a selected group of patients with a high predisposition to thromboembolic disease has been proposed as the only rational approach capable of saving patients who will otherwise die from this theoretically preventable complication.

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CARDIAC ARREST PRODUCED BY MASSIVE TRANSFUSIONS

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IN THE PAST TWO DECADES there has been an appalling increase in the reported incidence of cardiac arrest during surgery. According to Mozen and Beck, 1 in every thousand operations results in cardiac arrest. When one considers that there are 10,000,000 operations performed in the United States annually, the importance of this catastrophe cannot be overemphasized. Many factors have been implicated as etiologic in producing arrest, but there is no universal agreement as to the relative importance of each factor. Treatment has remained on an empiric basis because the etiology is not clearly defined. In our clinic, 2 cases of arrest following massive transfusion focused our attention on the relationship between blood transfusion and cardiac arrest. It is noteworthy that the increased incidence of cardiac arrest parallels the increased use of blood during surgery. The plasma concentration of potassium increases in bank blood during storage. By the end of 2 weeks, levels are reached 5 times as high as those found in normal blood. Was the rapid infusion of blood with a high potassium value the precipitating factor in the cases of cardiac arrest which are described in the following cases?

CASE 1. A 59 year old white male entered the Brooklyn Veterans Administration Hospital for an inguinal herniorrhaphy. On admission, physical examination revealed a pulsating abdominal mass. Six hours after admission he experienced severe abdominal pain and was taken to the operating room. Administration of blood was started, and a ruptured abdominal aortic aneurysm was found. The bleeding was controlled and the aneurysm resected. A teflon graft was inserted. The clamps occluding the aorta were released and brisk bleeding at the suture lines was seen. Blood was pumped in rapidly, as the bleeding was controlled. Suddenly, cardiac arrest occurred. Blood potassium drawn at this time was 8.7 milliequivalents per liter.

CASE 2. The patient had a massively bleeding peptic ulcer which did not respond to conservative therapy. He was operated upon within 24 hours after the onset of bleeding, and a subtotal gastrectomy was performed. While closing the abdomen, it was thought that blood loss during the episode had exceeded the amount transfused and an additional 1,000 cubic centimeters of bank blood was pumped in rapidly. Cardiac arrest occurred at this point. Blood potassium concentration at this time was 8.2 milliequivalents per liter.

The ability of the normotensive animal to maintain his serum potassium concentration even when large quantities of potassium are infused attests the efficiency of the homeostatic mechanism. It seemed possible to us that animals in hemorrhagic hypotension were more susceptible to potassium toxicity than were normal animals. This might account for the occurrence of cardiac arrest during massive transfusion, a situation which should be called "transfusion arrest." An experiment was devised in which animals were subjected to blood loss. Their resistance to potassium-induced cardiac arrest was then compared with normal animals. The protective action of potassium antagonists such as digitalis was also studied in these experimental animals. These experiments were designed to test the similarity between potassium intoxication and cardiac arrest occurring during rapid transfusion.

If this similarity does exist, would the animal be protected by potassium antagonists such as digitalis? The work of Szent-Gyorgi

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suggests that digitalis prevents potassium entry into the cell. Therefore, digitalis might offer protection against potassium-induced cardiac arrest.

If massive transfusion is an etiologic factor in producing cardiac arrest, surgeons must be alerted to this hazard and take the necessary steps to prevent this catastrophe. An inquiry into the nature of "transfusion arrest" and its clinical implications seemed mandatory.

LABORATORY METHODS AND MATERIALS

Twenty-five adult mongrel dogs were divided into 5 equal groups. All groups were fed a standard diet, but were fasted on the day of operation. Sterile perfusion solutions containing 40 milliequivalents of potassium chloride in 100 cubic centimeters of isotonic sodium chloride were prepared prior to the start of the experiment.

The animals were anesthetized with pentobarbital sodium (30 mgm./kgm.) administered intravenously. An endotracheal tube was inserted to insure a patent airway. Needle type electrocardiographic leads were attached to each limb. The left femoral vein was exposed in the groin. A No. 20 polyethylene cannula was inserted proximally into this vessel. Isotonic sodium chloride was slowly infused through this cannula. The left external jugular vein was exposed and a polyethylene catheter inserted through this vein to the atriocaval junction. A syringe containing heparin in saline was attached to this cannula and small amounts of this solution were injected periodically to keep the cannula patent. The right femoral artery was next exposed from the inguinal ligament to the midthigh. A bulldog clamp was placed on the proximal end and the distal end was ligated. A No. 14 polyethylene catheter was introduced proximally as far as the bulldog clamp and secured with silk ligatures. Blood loss during these procedures was negligible. Each animal was given 25 milligrams of heparin intravenously at this point. All animals except the control

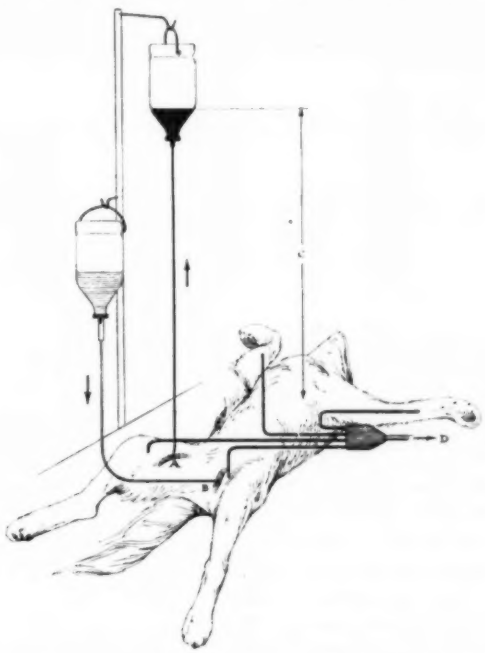

FIG. 1. The right femoral artery (*A*) and the left femoral vein (*B*) are cannulated. The animal is bled from the artery (*A*) into a heparinized bottle at a predetermined height (*C*) above the heart. The pressure at which outbleeding ceased is determined by this height (*C*). The electrocardiographic leads (*D*) are shown.

group (I) were allowed to bleed through the arterial cannula into a heparinized bottle which was at a predetermined height above the heart according to the method of Fine (Fig. 1). Groups II and III were bled to a pressure of 110 millimeters of mercury and groups IV and V to a pressure of 80 millimeters of mercury. Each dog in groups III and V received lanatoside C intravenously, 0.009 milligram per pound, 30 minutes prior to the onset of bleeding. When outbleeding had ceased, the pressure was checked with a mercury manometer. At this time the solution of potassium chloride (40 mEq./l.) was substituted for sodium chloride at a rate of 60 to 70 drops per minute. A continuous electrocardiogram was recorded on all animals from the onset of anesthesia until cardiac arrest. Blood samples were

FIG. 2. Lethal amount of potassium for individual animals in each subgroup is shown. There is a little variation within each group.

withdrawn from the atriocaval junction before the potassium chloride infusion began and at 4 minute intervals during this infusion. When cardiac arrest occurred as indicated by the electrocardiogram, the K+ infusion was immediately terminated and a blood specimen was withdrawn from the atriocaval junction. At the same instant a peripheral vein sample was drawn. All blood samples were promptly centrifuged to prevent hemolysis. and the serum (K+) was measured with the flame photometer. The amount of potassium chloride infusion needed to cause arrest was accurately recorded.

To study the effect of citrate in massive transfusion, 3 dogs were infused with acid-citrate dextrose solution. The dose used was 25 cubic centimeters per kilogram infused at a rate of 60 to 80 drops per minute. In the final experiment, potassium chloride was added to the anticoagulant acid citrate dextrose solution so that the concentration with respect to potassium was 40 milliequivalents per 100 cubic centimeters. This was infused into 3 normotensive animals by the method described for group I until cardiac arrest occurred.

TABLE I.—MEAN VALUES FOR POTASSIUM REQUIRED TO PRODUCE ARREST IN EACH OF 5 GROUPS

Group	*Mean weight, kgm.*	*Potassium required, mEq.*	*Control requirement, mEq./kgm.*	*Deviation from control, mEq./kgm.*
I	12.2	46.8	3.8	—
II	13.2	19.0	1.4	—2.4
III	14.1	49.7	3.6	—0.2
IV	11.4	16.6	1.4	—2.4
V	10.3	24.8	2.4	—1.4

Note that the lethal dose of potassium in the nondigitalized hypotensive animals (Groups II and IV) is the same.

RESULTS

The results of the 5 groups of animals are shown in Table I and Figure 2. The control group required an average of 3.8 milliequivalents of potassium per kilogram to produce cardiac arrest, with a range of 3.4 to 4.4 milliequivalents per liter. Group II (bled to 110 mm. Hg) required a mean of 1.4 milliequivalents of potassium per kilogram to produce arrest. In this group the amount of blood loss required to produce this pressure drop was less than 200 cubic centimeters. The electrocardiogram was no different from that of the control group. The use of a cardiac glycoside in group III raised the toxic dose to 3.6 milliequivalents per kilogram, not significantly different from the control value. It was observed during the outbleeding period that the stroke volume was greater in the digitalized animals, but the total amount of blood loss required to reduce the pressure to 110 was the same in groups II and III. This increased stroke volume was noticed also in group V. The average toxic dose in group IV was 1.4 milliequivalents per kilogram. Although these animals were bled to 80 millimeters of mercury, they were no more sensitive to potassium than the animals bled to 110 millimeters. The groups bled to 80 millimeters required a mean blood loss of 480 cubic centimeters to reach this pressure. The use of cardiac glycoside in animals bled to 80 millimeters (group V) raised the lethal dose of potassium to 2.4 milliequivalents per kilogram. This is an increase of 42 per cent over the lethal dose in the nondigitalized dogs.

The blood potassium levels for each 4 minute interval are shown in Table II. The levels are approximately the same in each group for the first 4 intervals. However, the digitalized groups required a larger amount

of potassium to reach the lethal level. The lethal potassium concentration measured immediately following asystole was the same in digitalized and nondigitalized animals. There is a disparity in blood potassium between the peripheral blood and that from the atrium. Figure 3 shows the relationship between blood potassium concentrations and total dose of potassium in groups IV and V. The amount of potassium required to produce arrest is higher in the digitalized group (group V), but the blood levels are the same in both groups.

The 3 animals receiving citrate alone revealed electrocardiographic changes similar to those found in animals receiving potassium. In no animal was cardiac arrest produced, even though large doses were used. These animals recovered completely, but were not used again in these experiments. In the 3 animals receiving potassium concurrently with the anticoagulant acid citrate dextrose solution, asystole developed with a potassium load of 2.5 milliequivalents per kilogram. This is less than the amount required by the control group which received potassium alone.

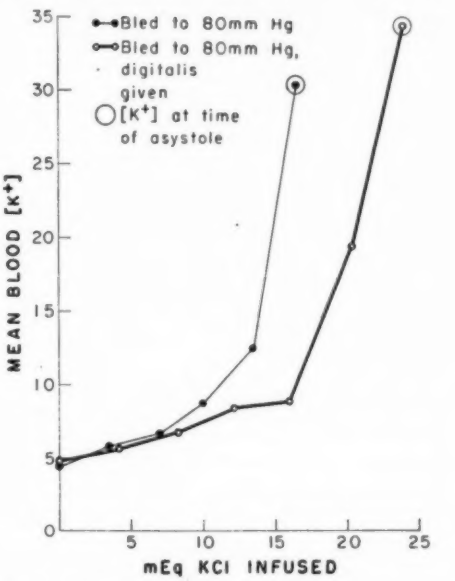

FIG. 3. Comparison of the serum potassium concentration as a function of the amount of potassium infused in groups IV and V. A greater amount of potassium is required to reach a given blood level in the digitalized group than in the nondigitalized group.

DISCUSSION

The results obtained are consistent with current beliefs concerning potassium metabolism. The increased sensitivity to potassium exhibited by bled animals was first shown by Zwemer and Scudder in 1938. These workers found that infusions of potassium chloride in normal dogs did not result in a marked change in plasma potassium concentrations. Animals in hemorrhagic hypotension, however, lost the ability to handle the potassium load and small infusions of this ion become toxic. Renal function is markedly decreased by hemorrhage, thereby eliminating an important mechanism for homeostatic removal of the infused potassium. Hypokalemia may occur during insulin therapy for diabetic coma because potassium is stored in the liver together with glucose. Anoxia or hemorrhage stimulates the liberation of adrenalin with resultant glycogenolysis. As glucose is released from the liver, potassium accompanies it. This is the reverse of the situation which occurs during insulin therapy for diabetic coma. Liver glycogenolysis, occurring during hemorrhage, liberates large amounts of potassium directly into the vena cava close to the heart. Hence, the heart and myocardium are suddenly perfused with blood having an extremely high potassium value which is in excess of that found in the peripheral blood.

TABLE II.—SERUM POTASSIUM CONCENTRATION (MEQ./LITER) IN SAMPLES DRAWN FROM THE ATRIOCAVAL JUNCTION AT 4 MINUTE INTERVALS DURING THE POTASSIUM INFUSION

Group	*0*	*4 mins.*	*8 mins.*	*12 mins.*	*16 mins.*	*20 mins.*	*24 mins.*	*28 mins.*	*Peripheral concentration*
I	4.9	6.3	6.8	9.2	11.2	16.0	27.7	*37.5*	10.6
II	4.6	6.5	8.3	11.2	15.9	*34.7*			9.9
III	4.5	5.9	7.1	10.9	13.8	20.4	*35.0*		9.0
IV	4.7	5.8	6.7	8.7	12.5	*30.5*			9.6
V	4.9	5.6	6.8	8.3	8.9	19.5	*34.3*		10.4

The serum potassium at the time of arrest was similar in all groups. The concentration of potassium in peripheral vein blood is also shown in a column at the right.

This central hyperkalemia may not be detected by analysis of samples of venous blood drawn from an extremity since this blood has already had the opportunity to equilibrate with the extravascular space. There are other factors which contribute to an increase in serum potassium during hemorrhagic hypotension and shock. There is a breakdown of cells due to anoxia and this liberates potassium into the serum. It has been shown that the radiosodium space during shock increases out of proportion to the thiocyanate space. This observation indicates that sodium gains access to cells from which it was formerly excluded. The converse is also true, which is that potassium leaves the cell as the sodium enters. Although there are a multiplicity of mechanisms which are involved, the decreased potassium tolerance shown by hypotensive animals has important clinical implications.

Dulière first drew attention to the fact that there is a rapid rise in serum potassium of stored blood. The fact that potassium is kept inside the cell and sodium is kept outside, despite the tremendous gradient, is evidence of a thermodynamic reaction which supplies the energy necessary to maintain this gradient. During refrigeration these energy mechanisms are sufficiently slowed so that an equilibrium tends to establish itself across the cell membrane. Cooling leads to an efflux of potassium from the cells into the serum. Incubation at 37 degrees C. for 6 to 8 hours will cause a return of this potassium into the cell. Hemolysis in properly stored blood is minimal during the first 21 days, and is not responsible for the rapid rise in serum potassium. The rise in serum potassium in bank blood stored under optimum conditions has been confirmed by us and is shown in Figure 4.

Our results clearly indicate that the animal in hemorrhagic hypotension is very susceptible to potassium arrest in concentrations which could be produced by the rapid infusion of bank blood.

In addition to the effects of cold on stored blood itself, lowering of the body temperature by cold blood alters physiologic responses. In most cases in which massive transfusion is required, blood is given within a few minutes of its removal from the refrigerator. This cold blood, if given in large amounts, will lower the temperature of the heart and great vessels out of proportion to that of the body. The sensitivity of the myocardium to arrhythmias is enhanced by hypothermia. This is another factor favoring transfusion arrest.

Melrose has pointed out the danger of potassium and cold blood in cases of intra-arterial transfusion. This route of administration is used only in profound shock and with large volumes of blood, so the hazards are intensified because the coronary vessels are directly perfused by the retrograde flow of this cold hyperkalemic blood.

The ability of the normovolemic animal to maintain a low serum potassium concentration while receiving large amounts of potassium in the infusion points out the efficiency of the homeostatic mechanisms. In the normovolemic state, excess potassium is excreted in the urine. Renal function is depressed during anesthesia, hypotension, and by hypovolemia. Under these conditions, potassium excretion cannot keep pace with the load presented by infusions of hyperkalemic blood. The liver removes potassium from the plasma and stores it as part of a complex glycogen molecule. Potassium storage occurs in other tissues in times of hyperkalemia, and this mechanism is of prime importance during surgery when renal excretion is suppressed. The liver no longer produces glycogen during anesthesia and hemorrhage, but liberates potassium as the stored glycogen is mobilized. Despite this failure in the mechanisms which normally control serum potassium levels, the animals maintained a nearly constant serum potassium concentration until circulation failed immediately preceding cardiac arrest. Zwemer and Scudder noted this also in their classic study on shock and potassium. They described this sudden preterminal hyperkalemia in both normal and shocked animals

but were unable to explain this phenomenon. The disparity between peripheral blood potassium levels and control (cardiac) levels has also been noted by these authors. Failure to appreciate that blood drawn from the antecubital vein may reveal a normal potassium concentration while blood perfusing the coronary vessels contains a lethal amount of potassium accounts for the lack of correlation between cardiac arrest and hyperkalemia in the literature.

Citrate has been implicated recently in many cases of "transfusion arrest." However, our work as well as that of Howland points out that citrate alone will not cause arrest in quantities which are clinically encountered even with massive transfusion. When administered rapidly, citrate causes an increase in QT interval, plasma potassium concentration, and total calcium. There is a temporary fall in ionized calcium, but this fraction is quickly replaced by calcium mobilized from bone. Howland believes that calcium need not be given along with transfusions, except in cases of severe hypotension. In these cases the mobilization of calcium from bone is impaired as blood flow to the bone decreases. We are of the opinion that calcium should be given in all instances of massive transfusion because its action is antagonistic to that of potassium. Citrate potentiates the toxic effects of hyperkalemia by temporarily reducing the ionized calcium. Myocardial function depends partially on the maintenance of a constant K^+/Ca^{++} ratio. Any factor which will disturb this equilibrium can produce adverse effects on the heart.

The use of digitalis to offset the toxic effects of potassium in stored blood was suggested by earlier work on the isolated turtle heart (5). Digitalis maintained the strength of cardiac contractions in the face of toxic potassium concentrations. The physiology of cardiac muscle as elucidated by Szent-Gyorgi offers an explanation of our findings. The cardiac toxicity of potassium is dependent on this ion reaching the intracellular actomyosin complex. This in turn depends on the permeability of the cell membrane. Digitalis, by preventing the passage of potassium into the cell, will enable the myocardium to function properly in the presence of toxic levels of this ion. The dog experiments show that digitalis offers significant protection against potassium-induced arrest. The clinical significance of this experiment is obvious. The routine use of digitalis in patients about to undergo major surgery when serious blood loss is anticipated may prevent "transfusion arrest." It is a practical and safe prophylactic measure. In reviewing our clinical material, it was noted that many of our patients undergoing vascular surgery have been digitalized for medical indications. This may explain the low incidence of arrest in this group in which large volumes of blood were rapidly transfused.

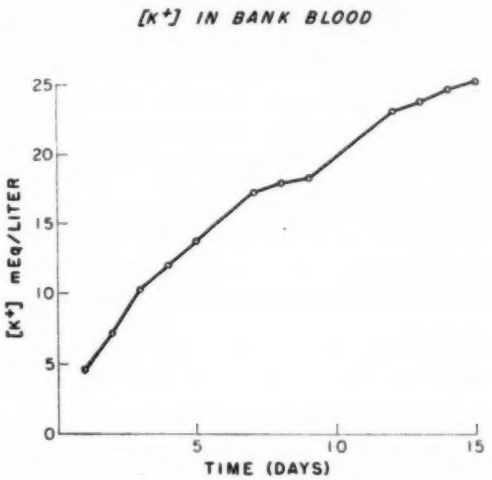

FIG. 4. The serum potassium has been measured daily in 10 specimens stored under optimum blood bank conditions. Toxic levels of potassium occur by the tenth day after collection.

To reduce the incidence of "transfusion arrest," the following suggestions are offered: (1) Do not allow blood loss to reach such proportions that vital signs change, making rapid replacement mandatory. An apparatus for instantaneous measurement of blood loss in the operating room has re-

cently become available and was described previously (4). Rapid transfusions can be avoided by slowly replacing blood as it is lost. Our recent experiments indicate that potassium excretion is impaired in compensated hypovolemia even though blood pressure and pulse rates remain unchanged. During compensated hypovolemia, serum potassium levels will rise with infusions of hyperkalemic blood. This elevation of serum potassium does not occur in normovolemic animals under identical circumstances. For this reason, it is essential that blood loss be replaced quantitatively as it is lost. The proper monitoring of blood loss relieves the surgeon of the responsibility for making hazardous estimates. (2) If possible, use fresh blood when massive transfusion becomes necessary. (3) Allow blood to equilibrate at room temperature before using. (4) Give calcium to counteract the effects of hyperkalemia. (5) In cases in which large blood loss is anticipated, a rapid acting glycoside may be administered prior to surgery.

SUMMARY

A type of cardiac arrest has been described which occurs during massive transfusion. The etiology of this transfusion arrest has been demonstrated to be similar to potassium intoxication. The high plasma potassium content of bank blood is contributory in producing transfusion arrest. Digitalis under our experimental conditions appears to offer some protection against cardiac arrest induced by potassium in hemorrhagic hypotensive dogs.

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FETAL BLOOD STUDIES

XVI. On the Changes in Total Osmotic Pressure and Sodium and Potassium Concentrations of Amniotic Fluid During the Course of Human Gestation

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IN THE RECENT PAST there have been many studies of the chemical composition of human amniotic fluid, and from these data hypotheses have been made as to its mode of formation. In addition, there have recently appeared reports concerning the changes in the amniotic fluid, as well as the other fetal fluid compartments, during the various stages of gestation in different animal species. For example, Alexander and associates found that the total osmotic pressure of the amniotic fluid of sheep fell as gestation advanced while that of the allantoic fluid increased. In their study, the change in total osmotic pressure of the amniotic fluid was found to be a gradual one and not limited to any particular period of gestation.

In a previous report from this laboratory (3), it was found that the total osmotic pressure and sodium concentration of fetal and maternal plasmas of human beings were virtually identical. It was also shown that any change in the composition of the maternal extracellular fluid was reflected in changes in the fetal extracellular fluid, although not necessarily in the same direction. Accordingly, a study of the changes occurring during gestation in total osmotic pressure and sodium and potassium concentrations of the human amniotic fluid was planned. It was believed that this would be helpful in giving more insight into the mode of formation of the amniotic fluid, and, in addition, would establish a better basis for understanding changes in amniotic fluid from intravenous fluids given the mother.

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MATERIALS AND METHODS

All patients were registered for delivery in the department of obstetrics at the Johns Hopkins Hospital. Samples of amniotic fluid were obtained at various stages of gestation, and the method of collection varied. Of the gravidas whose pregnancies had progressed to 37 weeks or beyond, 2 were delivered vaginally, and in these the amniotic fluid was sampled per vaginam by means of a long No. 20 gauge needle which was thrust through bulging membranes. In the 2 patients in whom the pregnancies had progressed to 35 and 32 weeks respectively (not in labor), the amniotic fluid was collected by inserting a needle through the anterior abdominal and anterior uterine walls. In all other patients, the amniotic fluid was sampled at laporotomy, either by means of a transuterine tap or by sampling the amniotic sac under direct visualization. Maternal samples were obtained from an antecubital vein at the same time as the amniotic fluid was collected. Since previous work from this laboratory had shown no difference between the maternal and fetal plasma total osmotic

TABLE I.—DATA OBTAINED ON THE TOTAL OSMOTIC PRESSURE OF MATERNAL PLASMA AND AMNIOTIC FLUID FROM THE THIRTY-FIFTH TO FORTY-FIRST WEEK OF GESTATION

Date of experiment	*Duration of gestation, wks.*	*Maternal plasma TOP*	*Amniotic fluid TOP*	*ΔTOP*
6-20-58	35	292.8	270.5	22.3
4-10-58	37	283.1	258.3	24.8
4-16-58	38	291.6	261.0	30.6
4-12-58	38	286.9	251.9	35.0
2-5-58	38	283.2	269.3	13.9
1-22-58	39	291.1	268.6	22.5
5-15-58	40	291.5	274.9	16.4
3-1-58	40	292.0	260.1	32.1
3-1-58	41	289.6	275.3	14.3
Average		289.1	265.5	23.5

TABLE II.—DATA OBTAINED ON THE TOTAL OSMOTIC PRESSURE OF MATERNAL PLASMA AND AMNIOTIC FLUID FROM THE NINTH TO THIRTY-SECOND WEEK OF GESTATION

Date of experiment	*Duration of gestation, wks.*	*Maternal plasma TOP*	*Amniotic fluid TOP*	*ΔTOP*
1-27-58	9	288.7	289.5	—0.8
4-10-58	14	—	286.0	—
1-29-58	15	292.3	286.3	6.0
5-7-58	19	288.4	284.8	3.6
6-19-58	32	288.0	289.2	—1.2
Average		289.6	287.2	1.9

TOP, the total osmotic pressure of the fluid in mOsm./kgm. of H_2O.
ΔTOP, the maternal total osmotic pressure—the amniotic fluid total osmotic pressure in mOsm./kgm. of H_2O.

pressures or sodium concentrations, only the data on the maternal plasmas are presented.

The specimens were drawn into oiled, heparinized syringes. The plasma was then separated from the red cells by centrifugation under oil and stored in oiled syringes at 4 degrees C. The total osmotic pressure was determined by the freezing point technique using a Fiske osmometer. This has an error of ±0.5 milliosmols per kilogram of water. The sodium and potassium concentrations were determined by flame photometry, using a Patwin flame photometer and lithium as the internal standard. The error in the sodium determinations was ±3.0 milliequivalents per liter of plasma, and in the potassium determinations, ±0.1 milliequivalent per liter of plasma.

RESULTS

The changes in the total osmotic pressure of the amniotic fluid during the course of gestation. The results of all determinations are arranged into two groups. The basis for this subdivision is the duration of pregnancy. In group I are included all cases in which the period of gestation was 35 weeks or more. The data from these cases (9 in all) are presented in Table I. In every instance the amniotic fluid is markedly hypotonic with respect to the maternal plasma. The average value for the total osmotic pressure of the maternal plasma is 289.1 milliosmols per kilogram of water and for the amniotic fluid, 265.5 milliosmols per kilogram of water. It can also be seen that within this period of 35 to 41 weeks' gestation, there is no consistent trend in the total osmotic pressures of the amniotic fluid.

The second group consists of the 5 cases in which the gestational period varies from 9 to 32 weeks. These data are presented in Table II. The average maternal plasma total osmotic pressure for this group is virtually identical with that in Table I. The striking difference, however, occurs in the total osmotic pressure of the amniotic fluid which is practically isotonic with the maternal plasma. Hence, the change from isotonicity to hypotonicity of the amniotic fluid appears to occur between the thirty-second and thirty-fifth weeks of gestation. No attempt has been made to limit further the period of gestation over which this change occurs since a 3 week span encompasses our accuracy in estimating gestational age.

The data for the total osmotic pressure changes in the amniotic fluid in all cases are given in graphic form in Figure 1.

The changes in the sodium and potassium concentrations of the amniotic fluid with increasing gestation. These observations are also presented in two groups. The data representing the cases of from 37 to 41 weeks' gestation are presented in Table III and of from 9 to 19 weeks in Table IV.

As seen in Table III, in 7 patients the average sodium concentration of the amniotic fluid (from the thirty-seventh week of gestation onward) is 125.3 milliequivalents per liter of plasma, and the average potassium concentration is 4.0 milliequivalents per liter of plasma. The average maternal plasma sodium and potassium concentrations over this same period are 138.0 milliequiva-

lents per liter of plasma and 3.5 milliequivalents per liter of plasma, respectively. On the other hand, (Table IV) the average sodium concentration of the amniotic fluid in the 4 cases of from 9 to 19 weeks' gestation is 137.4 milliequivalents per liter of plasma, and the potassium concentration is 4.0 milliequivalents per liter of plasma. Hence, the pattern of change in the sodium concentration with increasing gestation resembles that of the total osmotic pressure.

By making the assumption that the sum of the sodium and potassium concentrations approximates the cationic concentration of the amniotic fluid, it is possible by means of the following equations to test the hypothesis that the observed total osmotic pressure changes are due primarily to changes in electrolyte concentration:

$$(1)\ \left[[Na]_M+[K]_M\right]-\left[[Na]_A+[K]_A\right]=\Delta C$$

Assuming the change in amniotic fluid electrolyte concentration to be due to monovalent ions, then:

$$(2)\quad 2\Delta C \cong \Delta TOP$$

where:

$[Na]_M$ = maternal plasma sodium concentration in mEq./liter of plasma.
$[K]_M$ = maternal plasma potassium concentration in mEq./liter of plasma.
$[Na]_A$ = amniotic fluid sodium concentration in mEq./liter of fluid.
$[K]_A$ = amniotic fluid potassium concentration in mEq./liter of fluid.
ΔC = difference between the major cationic concentrations of maternal plasma and amniotic fluid.
ΔTOP = difference between total osmotic pressures of maternal plasma and amniotic fluid.

The extent to which equation (2) holds true would then be an index of the validity of the above hypothesis.

Applying this line of reasoning to the observations in group I, in which the amniotic fluid is hypotonic, one finds upon substitution of the average values into these equations that $\Delta C=12.2$. Equation (2) then becomes: $24.4 \cong \Delta TOP \cong 23.5$.

Applying these same equations to the experiments in group II, then $\Delta C=0.1$ and equation (2) becomes: $0.2 \cong \Delta TOP \cong 1.9$. Thus, apparently, the changes in tonicity of the amniotic fluid can be ascribed mainly to changes in its electrolyte concentration.

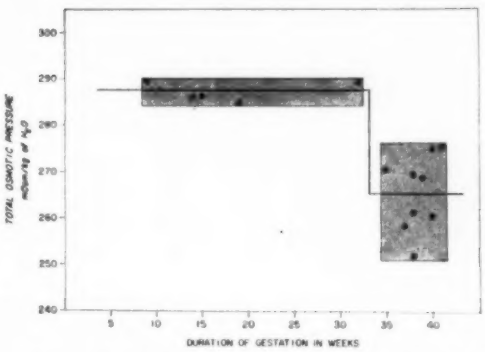

FIG. 1. The changes in the total osmotic pressure of the amniotic fluid during the course of human gestation.

DISCUSSION

In this report an attempt has been made to demonstrate the changes in tonicity and electrolyte concentration in human amniotic fluid throughout the course of gestation. As a comparison maternal plasma has been employed, since in previous studies the relationship between these parameters and the maternal and fetal plasmas was established. From the data obtained it appears that the major changes in sodium concentration and total osmotic pressure of the amniotic fluid in humans are limited to one period of gestation, i.e., between the thirty-second and thirty-fifth weeks.

The animals that have been most studied to date relative to this problem have been sheep and goats. Alexander and associates found the total osmotic pressure of the amniotic fluid to fall to hypotonic levels gradually during gestation, the change in total osmotic pressure not being limited to any particular period. Furthermore, they reported no corresponding change in the sodium and potassium concentrations; hence, the total osmotic pressure change remained unaccounted for in their series. Barron and associates, in a larger series of animals, also found a gradual change in the total osmotic pressure of the amniotic fluid of sheep and goats but were able to account for this

TABLE III.—A COMPARISON BETWEEN THE SODIUM AND POTASSIUM CONCENTRATIONS OF AMNIOTIC FLUID AND MATERNAL PLASMA IN HUMAN GESTATION—37 TO 41 WEEKS

Date of experiment	*Duration of gestation, wks.*	*Maternal plasma Na*	*Amniotic fluid Na*	*Maternal plasma K*	*Amniotic fluid K*
4-10-58	37	139.0	119.5	—	3.9
4-16-58	38	138.0	122.6	3.9	4.1
4-12-58	38	140.0	123.8	2.9	3.3
2-5-58	38	133.6	128.4	3.3	4.0
1-22-58	39	141.0	133.0	3.6	4.2
3-1-58	40	135.5	120.6	3.4	3.8
3-1-58	41	139.0	129.0	3.9	4.6
Average		138.0	125.3	3.5	4.0

TABLE IV.—A COMPARISON BETWEEN THE SODIUM AND POTASSIUM CONCENTRATIONS OF AMNIOTIC FLUID AND MATERNAL PLASMA IN HUMAN GESTATION—9 TO 19 WEEKS

Date of experiment	*Duration of gestation, wks.*	*Maternal plasma Na*	*Amniotic fluid Na*	*Maternal plasma K*	*Amniotic fluid K*
1-27-58	9	—	138.4	—	4.3
4-10-58	14	—	134.7	4.3	4.6
1-29-58	15	141.9	139.3	—	3.7
5-7-58	19	137.5	137.0	3.1	3.4
Average			137.4		4.0

Plasma Na, plasma sodium concentration in mEq./liter of plasma.
Plasma K, plasma potassium concentration in mEq./liter of plasma.
Amniotic fluid Na, amniotic fluid sodium concentration in mEq./liter of fluid.
Amniotic fluid K, amniotic fluid potassium concentration in mEq./liter of fluid.

change in osmotic pressure by a corresponding change in sodium and potassium concentrations. Since the ungulate has a different fetal and placental morphologic structure from that of the human (e.g., these animals have, in addition to the amnios, an allantoic fluid compartment), it may well be that the differences between human and ungulate observations can be accounted for by differences in the mode of formation of the amniotic fluid in these species. At any rate, in all species, the total solute concentration of the amniotic fluid appears to be declining as gestation advances.

Finally, those who have employed tracer techniques in an attempt to study the transfer of water and electrolytes across the placenta and into the amniotic fluid have come forth with no information regarding net volume changes in solutes and water in the various fetal compartments. A previous report from this laboratory presented data showing the effect of intravenous fluids given to the mother upon the plasma total osmotic pressure and electrolyte concentrations of the fetus. This study of the normal gestational changes of the amniotic fluid is presented preparatory to a study, similar to the previous one, of the effect of fluids given to the mother upon the total osmotic pressure and electrolyte concentrations of the amniotic fluid as well as the fetal plasma (3).

SUMMARY

The total osmotic pressure and sodium and potassium concentrations of the amniotic fluid have been compared with those of the maternal plasma throughout the course of gestation. As pregnancy advanced, the total osmotic pressure and sodium concentration of the amniotic fluid fell to values approximating 265.0 milliosmols per kilogram of water and 125.0 milliequivalents per liter of fluid, respectively. Comparable maternal plasma values for total osmotic pressure and sodium concentration were 289.0 milliosmols per kilogram of water and 138.0 milliequivalents per liter of plasma, respectively. These changes in the amniotic fluid occurred between the thirty-second and thirty-fifth week of gestation. The potassium concentration remained constant throughout pregnancy, averaging 4.0 milliequivalents per liter of fluid, approximately 0.5 milliequivalent per liter of fluid higher than that of the maternal plasma.

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EDITORIALS

THE FUNCTIONS OF A METROPOLITAN HOSPITAL

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Most of our present metropolitan teaching hospitals started modestly as small institutions for the care of the sick and poor. In accordance with the custom and the times, the original medical staffs were composed largely of general practitioners from the community. As time passed, the medical staffs became divided into partial specialists, and later fully specialized departments and subdepartments developed.

This change resulted in a gradual loss of the general practitioner from the urban staff. He sometimes referred patients to the general hospital's clinics, or to individual specialists for care in the field of their specialty. More often he established his hospital connections with the smaller, nonteaching city or suburban hospitals which were: (1) willing to accept him upon their staff, and (2) much more accessible to the homes of his local patients.

Many of the specialists of the teaching hospital staff lost direct contact with the community population through this process. The exceptions were largely among the internists and the pediatricians. These two groups, through their offices and home care of the patient, retained closer contact with the general community.

With the exception of patients of these two groups, the hospital population grew to be composed of patients referred for a specific disease or procedure, the self-referred who were dissatisfied with their previous care or who did not know where otherwise to obtain medical care, and a large local group who attended clinics, free or pay, and grew to depend upon the hospital as an institution rather than upon an individual physician.

With the growth of the communities, many of the better metropolitan hospitals added teaching of undergraduate and graduate medical students. Increasingly they have added facilities for research by their clinical staff and more complex facilities and personnel for basic research in the fundamental sciences.

There is no question but that these developments are good. The addition of these facilities has been useful for society in the larger sense. It has been of great advantage to the individual who is a patient in such a hospital, and it has served to stimulate the development of the younger group of physicians who are selected to serve upon the staff of such a hospital.

The structure and function of the university teaching hospitals have tended to follow this same pattern with only slight difference in methods of patient acceptance, and in the manner of medical staff support. Both types of hospitals select their junior staff on the basis of promise with regard to their prospect as teachers of medicine and as possibly productive investigators.

The university hospital has generally accepted the fact that much of the financial support of the staff is a function of the university. Increasingly, the voluntary hos-

pital is accepting the same function. Such support has always been a necessity for the nonclinical portion of the staff. It appears increasingly desirable for the segment of the senior staff whose time is largely occupied in teaching or administrative duties. Until recently, such support has not been required for most of the clinical staff.

In many of the clinical specialties, but particularly in general surgery and the surgical specialties, the voluntary hospital has found that if it is to retain upon its staff younger men of promise it is necessary for a time that they be offered some sort of subsidy. There is little contact between most junior surgeons and the community. The centripetal growth of the cities and suburbs has seen to that. The local community hospitals and the increasingly good suburban hospitals care for the patients he once would have had.

A generation ago this problem was met with partial adequacy by the custom of assistantship or associateship with an older clinician. The wide development of residency programs in the larger voluntary hospitals has made this method archaic. The associate is no longer needed as an assistant. He now is of only slight help in the conduct of the clinic and dispensary; and he may, if given improper function, actually interfere with the training mechanism of the residency program.

Efforts have been and are being made to meet the support of the younger surgeon through the establishment of hospital staff clinics for paying patients. This has been only partially successful. In many situations his support has depended upon endowment funds, fellowships, or, less desirably, upon hospital income from patients.

From the viewpoint of the patient's total needs, the voluntary metropolitan hospital or the university teaching hospital is not adequate. The patient is well cared for during his acute illness. He often is well cared for if he can and should be ambulatory. Between these states is a hiatus. He has come to regard the general hospital, incorrectly, as his physician. If he needs care for relatively minor illnesses or procedures he must change his medical and institutional relationships; or often he is admitted to the hospital which is geographically inconvenient and too expensively staffed and equipped for the needs of this illness or procedure. Conversely, he occupies a bed the community needs for a more serious condition.

Many urban hospitals which must maintain good departments of obstetrics and pediatrics to fulfill their teaching function and to have good consultation available in these fields are finding the maintenance of such departments difficult for these reasons. This trend will increase and may spread to other medical specialties. And yet the general hospital must remain truly a general hospital for its teaching and research functions and for its function in the care of severe and complicated conditions.

Only a partial solution, and this only from the standpoint of the patient's needs and not from the need of the general hospital, is the addition of home calls to the function of the hospital staff. The shifting character of urban populations makes it of limited long term utility. The working wife and the disappearance of the large family group have made home care of all but the most minor illnesses impractical. There is a great group of diseases which requires adequate institutional and professional care, but which does not need the elaborate equipment and personnel and research facilities of the urban teaching hospital.

The urban hospital needs patients in this category for its teaching program. It needs them for the junior stages of its residency program. It needs them for the support in private practice of its junior staff. At the same time the patient or his insurance company should not bear a portion of the expenses of elaborate facilities, the geographic inconvenience, and the uncertain communications with the urban hospital and its insulated staff.

A local nursing home is an inadequate solution. Its facilities are limited, and serious

illness or complications of existing illness would require transfer and loss of continuity of care. The urban and suburban type of community hospital is doing an increasingly competent job. It does so by most expensively duplicating all of the physical facilities of any general hospital. It has difficulty in maintaining an intern or resident staff, and at the same time it is increasingly caring for the obstetric and more routine surgical procedures needed by the urban general hospital for teaching and training purposes. Its staff may lack the stimulus for development of the general hospital.

A possible solution of these problems is as follows: The general hospital can well establish a reasonable number of urban and suburban divisions. These would be administered by the central hospital. Interns and residents could be rotated through the branches when the training facilities justified it.

The branches should be constituted with an appropriate small number of beds for in-patient care, and with nursing, dietary, and housekeeping service adequate to care for normal obstetrics, most pediatrics, ordinary internal medical problems, and types of surgical care in which the possibility of complicated or serious problems should not arise.

There should be a dispensary, physicians offices, and facilities for routine laboratory and the simplest x-ray service. A station wagon ambulance can transport patients and specimens for the more elaborate diagnostic procedures to the central hospital when indicated. Patients could be as easily returned to the branch for convalescence.

The medical staffing would be made by the central hospital. The staff would serve generally on a private practice basis, using a part time or appointment system, and with provision for emergency and for consultation service from the central hospital when requested. Appropriate modifications could be made in the design to suit the need and character of the community served by the branch.

A design of this type would serve desirable objectives:

1. It would supply more nearly total care and good medical care to the communities served.

2. It would supply teaching and graduate training facilities in fields now disappearing from the urban general hospital.

3. It would make available to a much larger group than is now receiving them the facilities and competencies of the urban hospital and its staff.

4. It would serve to support a group of younger staff physicians during their earlier productive years without disrupting their teaching and investigative functions in the central hospital.

5. It would avoid extension of the present extensive duplication of facilities in general and community hospitals, afford certainly more extensive and possibly more reliable supervisory, diagnostic, and consultation service; and at the same time it should reduce the cost and improve the medical care to the patient.

THE FAILURE OF NERVE BLOCK IN POSTOPERATIVE INTERCOSTAL NEURALGIA

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MOST SURGEONS are familiar with the patient, who, after an elective transthoracic operation, complains of unrelenting chest wall pain. Few patients require more professional time and receive less satisfaction than those who suffer from postoperative intercostal neuralgia. The persistent pain eclipses all of the preoperative symptoms; the rewards of the operation as well as the patient's gratitude are submerged by the torments of this subjective disease.

Anticipation of a painful incision in the chest has diverted many surgeons toward the transabdominal route for operations that might best be accomplished above the diaphragm. Thoracic surgeons have tried to alleviate this problem by improved surgical techniques. Some have advocated rib resection and meticulous attention to its periosteum; others have endorsed the intercostal approach in which no rib is cut, fractured, or excised. The gamut of complementary nerve procedures has been run and rerun. Intercostal nerves and portions of the adjacent sympathetic chain have been sacrificed in the hope that abolition of painful pathways would prevent this complication. The sad fact remains that no trickery of technique offers insurance against postoperative intercostal pain.

Postoperative incisional neuralgia prompted the use of intercostal nerve block for prophylaxis and therapy. The rationale of this treatment was not questioned even though the exact nature of intercostal neuralgia is not understood. The popularity of intercostal nerve block has stimulated the search for a long-acting chemical agent that would offer complete, or at least prolonged, relief of pain. To date, this search has been costly both to pharmaceutical houses and to those surgeons who have sustained legal repercussions after using chemical agents that served to compound the problem. It is now apparent that intercostal nerve block during or after operation does little to prevent this unpleasant complication.

The etiologic mechanism of intercostal neuralgia after elective thoracic surgery is not understood. It is unlikely that the disease can be explained on the basis of traumatic neuroma or compression of the involved intercostal nerves. If operative trauma and the resultant scar formation were responsible factors, then this complication would develop in all patients who undergo thoracic surgery. But postoperative intercostal neuralgia is almost unheard of in children and adolescents; moreover, neuralgia is unusual in those adults who have been operated upon for malignant disease of the thorax or for serious forms of heart disease. Although the operative approach in the treatment of neoplastic and cardiac disease is more extensive than that employed for most benign conditions these patients are usually pain-free within a few weeks. Excepting children, it would seem that the patients least likely to have intercostal neuralgia are those who psychologically accept operation as the key to ultimate survival. In contrast, we see troublesome neuralgia in those adults who undergo elective thoracic surgery for a benign condition, in particular, the patients who have required persuasion by their consultant physicians.

Reaction to postoperative discomfort varies with individual patients. For understandable reasons, the surgeon is reluctant to depend entirely on narcotics, particularly

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those given by hypodermic techniques, so after the first week he will seek other methods to control pain. The patient who makes greater demands and tries the patience of his attending physicians is more likely to have additional therapeutic measures. In other words, the patient who complains most bitterly will receive an extra bounty of the surgeon's sympathy and skill. This is the patient, and the time, for the first intercostal nerve block as treatment of troublesome incisional pain. Whether this added treatment is given by the responsible surgeon himself or by a consultant anesthesiologist or neurosurgeon, the result is basically the same—a brief period of pain-free numbness, then painful rebound which restores the original situation. A second therapeutic nerve block may follow; this one more meticulously and more elaborately performed than the first, but with the identical end result. Intercostal neuralgia now is fixed in this particular patient, and all signs point to a long, relentless course that will plague the patient, his family, and surgeon.

A critical evaluation of intercostal nerve block for the prevention and treatment of incisional neuralgia following thoracotomy is long past due. Whereas the logic of intercostal nerve block was sufficient grounds to justify its clinical use, it now appears that transient relief of incisional neuralgia is the most that can be expected from this procedure. The concept of breaking a pain cycle by anesthetic interruption of the nerve pathways is whimsy. The long-acting anesthetic agents add little, as their effect is measured in hours or days while the complication seemingly goes on forever. Diligent study of excised intercostal nerve fragments has not established a recognizable nerve disease; this brings the surgeon back to the basic point that it is hard to treat a disease that may not exist in an organic state.

If postoperative incisional neuralgia is a subjective disease with little organic manifestation, then suggestion may be an important factor in its causation. It is in the immediately postoperative period that the patient is alerted to the value of pain. Should the patient conclude, either consciously or subconsciously, that there exists a quantitative relationship between pain and the quality of care, then trouble is in the offing. If this concept is extended to include duration of postoperative disability, the problem is compounded. If the attending surgeon and his associates are not alert, the painful thought which now enters the patient's mind may be the forerunner of an unpleasant fixed idea. The solicitous resident and nursing staff must remember that the abuse of sympathy, like the abuse of a drug, may set the stage for chronic disability.

The greatest indictment against intercostal block for the treatment of incisional pain is the response of the patient. An informal questionnaire presented to anesthesiologists, neurosurgeons, and thoracic surgeons, reveals that the patient's demand for a second intercostal block is somewhat unusual—the patient's demand for a third nerve block is an almost unheard of phenomenon. The majority of patients who undergo intercostal block reject the idea of a second or third treatment because the "rebound pain" exceeds the original subjective pain. It is generally conceded that the same patient who refuses the intercostal needle will accept gratefully a hypodermic needle.

There is no simple answer to the problem of residual incisional pain after transthoracic operation. Nevertheless the experienced surgeon should anticipate that patient who is most likely to develop and to nourish this subjective disease. Incisional pain, during the first postoperative days, must be accepted as a normal accompaniment to any operative procedure. However, precautions must be taken to avoid fixation of the painful incision upon the receptive patient. This is best accomplished by the surgeon's basic approach, in which firmness, understanding, and a modicum of sympathy are combined. On the basis of past experience it is quite likely that the use of intercostal nerve block does more to perpetuate incisional pain than it does to treat or to prevent it.

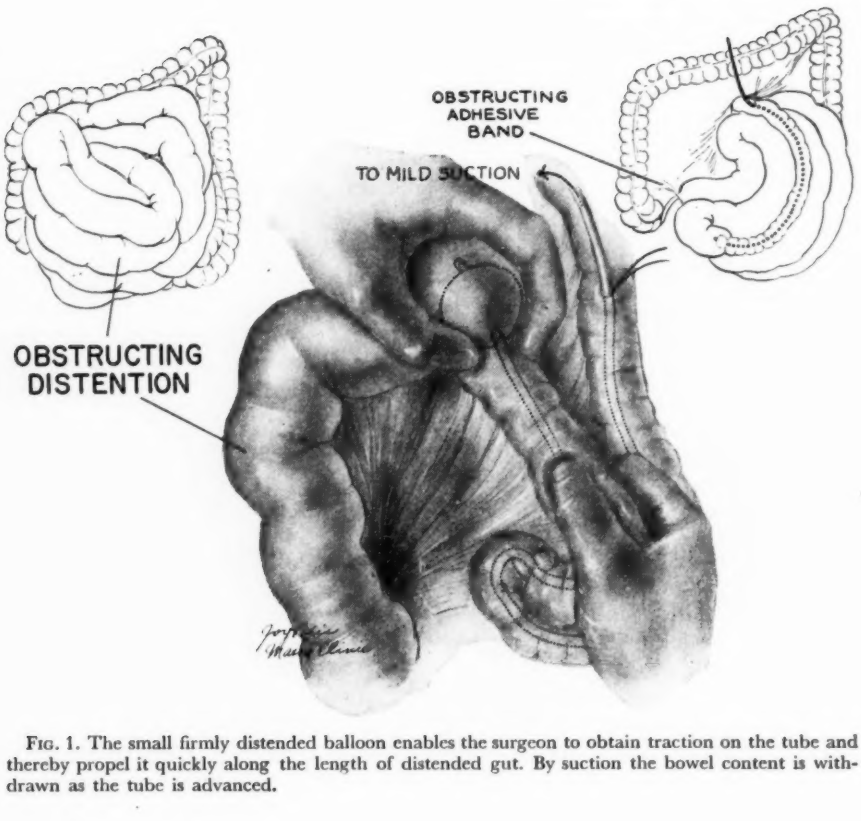

FIG. 1. The small firmly distended balloon enables the surgeon to obtain traction on the tube and thereby propel it quickly along the length of distended gut. By suction the bowel content is withdrawn as the tube is advanced.

A Long Jejunostomy Tube for Decompressing Intestinal Obstruction.—Joel W. Baker.

THE SURGEON AT WORK

A LONG JEJUNOSTOMY TUBE FOR DECOMPRESSING INTESTINAL OBSTRUCTION

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In operating for obstruction it is essential to decompress the dilated bowel as well as to free the obstruction. Each surgeon has his own method of emptying the distended gut. Too often, for lack of an effective method, a needle or short catheter is used to aspirate but a single loop, whereas the distention involves the entire length of the gastrointestinal tract proximal to the obstruction. The remainder of this distended bowel is left unrelieved and recovery is thereby delayed. Not only does the toxic luminal content remain to impede the patient's recovery but the continued distention impairs the circulation of blood through the wall of the intestine and interferes with the recovery of peristalsis. Furthermore, closure of the abdominal wound is awkward because of this distention. It is as physiologically important to empty the bowel as it is by parenteral administration to replace the fluid and electrolyte loss therein. The patient with unrelieved obstruction of the small intestine dies of distention even if electrolyte and fluid support are adequately maintained. It is, therefore, important to decompress the entire length of distended, edematous bowel from Treitz' ligament to the point of obstruction. Furthermore, this should be done before the adhesion is freed. Otherwise, if the knife-like adhesion has compromised the bowel wall, rupture at this site may follow when the adhesion is freed, and massive spillage may result.

In such situations a long catheter is inserted through a purse-string opening in the upper jejunum about 1 foot distal to the ligament of Treitz and, with this catheter connected to low pressure suction, it is advanced down the intestine, evacuating the gas and liquid content all the way to the point of obstruction. Various tubes were tried in attempts to accomplish this with facility and minimum trauma to the edematous intestine. A tube with a balloon at the end works best. This balloon serves to permit the surgeon to pull the tube and to thereby advance the tip of the tube as the intestine is gently stripped and aspirated free of content (Fig. 1). This tube is inserted into the jejunum a foot below the ligament of Treitz through a purse-string suture. This purse-string suture is tightened, the balloon is inflated, and the tube connected to low pressure suction. For this purpose, the tube must have a balloon which, when tightly distended to make it firm, is smaller in diameter than the gut. A balloon 1 inch in diameter suffices. The suction holes must be in a short, soft nosed tip beyond the balloon in order to decompress by suction as the tube is advanced. The tip must not extend more than one-half inch beyond the balloon as a longer nose will catch and kink in the folds of mucosa. The tube should be of soft latex rubber with the greatest possible proportion of its cross section devoted to lumen. The standard Bard-Foley urethral catheter fulfills these requirements except that it is only 17 inches in length, and it is obviously impossible to thread 26 feet of ileum upon such a short tube. Recently we have had a latex balloon catheter of extra length made specifically for this purpose. The catheter is made 40 inches long although a 60 inch length would be preferable. This long catheter is available in 2 calibers, 20 and 24 French (Fig. 2).

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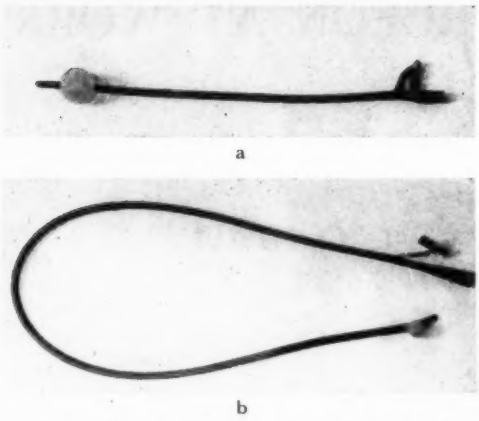

a

b

FIG. 2. a, Standard Bard-Foley urethral catheter 17 inches in length. b, Same type catheter 40 inches long used in decompressive jejunostomy.

Since the catheter opening is large and distal to the balloon, the intestinal content is aspirated easily by suction as the tube is advanced. After the level of obstruction is reached, the balloon is deflated. The small intestine is now pleated upon the length of this long tube which is left indwelling near the site of obstruction. The upper end of this tube is brought out according to the method of Witzel through a stab incision in the upper left flank. The jejunum is anchored to the peritoneum at the site of exit of the tube with several silk sutures (Fig. 3). This tube is gradually withdrawn during the next 5 to 7 days as the patient has normal bowel movements.

When jejunostomy is used for decompression, it must be remembered that it does not empty the stomach. If the stomach is also in need of suction, it is more comfortable to the patient to perform concomitant tube gastrostomy so that the untoward sequelae of prolonged nasogastric suction—discomfort, pharyngitis, and aspiration pneumonitis—can be avoided.

It should be added that there is an occasional place for laparotomy and the use of this special tube in the protracted adynamic or paralytic ileus. This is true if the long nasogastric tube cannot be successfully advanced beyond Treitz' ligament, and intestinal distention has become sufficiently severe that the bowel no longer has a chance to recover without the aid of mechanical decompression. In fact, such increasing distention may create a volvulus around the mesentery and thereby superimpose a mechanical obstruction upon the initial ileus. The treatment of paralytic ileus, in general, is not by operative surgery but rather by long nasogastric tube suction, electrolyte support, and attention to the underlying etiologic condition. Nevertheless, if the intestinal distention is not relieved, the patient can die of the effects of distention just as in mechanical obstruction. Furthermore, the more advanced the distention the more difficult it becomes to pass the Miller-Abbott or other long tubes. When this situation prevails and attempts at passing the long nasogastric tube are unsuccessful, we would then as in the case of mechanical distention, surgically decompress the distended bowel as already described. Here too it is essential to decompress the entire length of gut down to the ileocecal valve, and not just a single loop, and in this instance too the bowel would be left threaded on the long tube, brought out through a stab incision, until stools by rectum attest a restoration of peristalsis. By this method moribund patients have been seen to recover.

FIG. 3. The small intestine has been pleated upon the length of the long tube. The balloon has been deflated and the proximal end of the tube is brought out through a stab incision in the upper left flank according to the method of Witzel. The tube is gradually withdrawn during the next 5 to 7 days as the patient has normal bowel movements.

THE UTILITY OF URETEROILEAL URINARY DIVERSION IN THE TREATMENT OF IRREPARABLE URETERAL OBSTRUCTIONS

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DISTAL URETERAL obstructive uremia usually is treated by nephrostomy. Although the manifestations of uremia are relieved and further obstructive renal damage prevented by bilateral nephrostomy or cutaneous ureterostomy, neither method affords satisfactory permanent ureteral diversion. The following cases demonstrate the efficacy and safety of ileal-segment ureteral urinary diversion as the primary treatment for ureteral obstructive uremia in patients having irreparable lower urinary tract disease.

CASE SUMMARIES

CASE 1. M. C., an 18 year old female, had had an adenocarcinoma of the rectum. Resection of the neoplasm which had not metastasized to the liver or periaortic lymph nodes required the removal of the uterus, posterior vaginal wall, and rectum. The cancer had extended beyond the rectal wall and was found in 12 of 65 lymph nodes. Three weeks postoperatively transitory pyelonephritis developed, and the left renal collecting system was found to be hydronephrotic. Sixteen months later, pyelonephritis again developed. This time the left renal collecting system could not be demonstrated by intravenous pyelography (Fig. 1), and there was severe pelvic pain. A cervical cordotomy was performed which relieved the pain for 7 months. Pain then began on the left side of the abdomen and in the back.

She was now oliguric and had not urinated for 3 days, was very restless, and was somewhat disoriented. She had ventricular tachycardia (Fig. 2) with a pulse rate of 150 to 160 per minute, a blood pressure of 160/110 millimeters mercury, generalized hyperactive tendon reflexes, a nonprotein nitrogen concentration of 180 milligrams per cent, and a serum potassium concentration of 10 milliequivalents per liter. This determination was repeated immediately and found to be correct; the specimens of blood examined were free of hemolysis. Twenty per cent glucose in water intravenously and several enemata containing a cation exchange resin (sodium polystyrene sulfonate) were given. Serum potassium concentration 12 hours later was 7.6 milliequivalents per liter and the electrocardiographic findings were negative. An attempt was made to establish upper urinary tract drainage through ureteral catheters but this failed.

Ileal-segment urinary diversion was then effected (Fig. 3). Persistent adenocarcinoma had invaded the sacrum and was obstructing the ureters in the pelvis. No other tumor was seen. The left ureter was found to be obstructed by both tumor and scar. Ten liters of urine were excreted during the first 20 postoperative hours and improvement was rapid. Serum potassium and nonprotein nitrogen concentrations soon dropped to normal.

Two weeks postoperatively miokon sodium was rapidly excreted by the right hydronephrotic kidney but none by the left. Subsequently, repeated intravenous pyelograms showed regression of right hydronephrosis and a partial return of dye excreting capacity in the left kidney (Fig. 1). Postoperatively, irradiation therapy (betatron) was directed to the persistent carcinoma in the pelvis. She remained free of pain and urinary symptoms for 11 months. Obstructive uremia associated with abdominal carcinomatosis resulted in death 12 months after the ureteroileal diversion.

CASE 2. A. G., a 48 year old woman, received irradiation therapy for squamous cell carcinoma of the cervix (League of Nations III). Intravenous and retrograde pyelography before irradiation showed a hydronephrotic right kidney having no visible excretory capacity; the left kidney was normal. Eight months later, it became evident that the carcinoma persisted and she had pyelonephritis and azotemia. Retrograde pyelography showed left hydronephrosis, grade III. The right ureter could be catheterized no longer. Vaginally, a large ulcerated mass extended to both pelvic walls. Complete anuria followed the removal of the left ureteral catheter which had been left in situ for 5 days after retrograde pyelography but had not effected sufficient relief of the obstruction to permit recovery from uremia. She was still drowsy and had a serum nonprotein nitrogen concentration of 100 milligrams per cent. Her blood pressure was 120/90 millimeters mercury and pulse rate 144 per minute. Thereupon, emergency exploration of the abdomen was performed. The tumor was found to be confined to the pelvis. An ileal-segment ureteral diversion was carried out. Subsequently, the serum nonprotein nitrogen concentration quickly dropped to 21 milligrams per cent. Eighteen days after the ileal-segment urinary diversion, a complete exenteration of the pelvic organs was performed. Eighteen days later, intravenous pyelography showed

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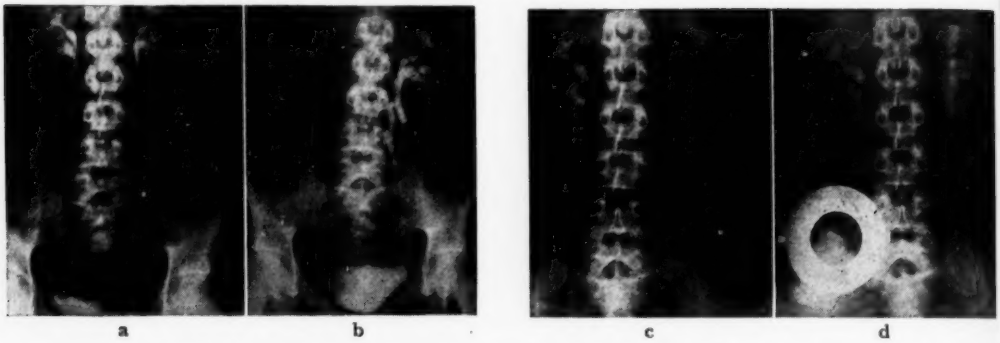


a b c d

FIG. 1. Case 1. Representative intravenous pyelograms show: a, Preoperative normal renal collecting systems. b, Left hydronephrosis 3 weeks after resection of the rectal carcinoma. c, No excretion of miokon sodium by the left kidney 16 months after rectal resection (7 months subsequently ureteroileal urinary diversion was performed for ureteral obstructive uremia). d, A normal right and a hydronephrotic left kidney 7 months after urinary diversion.

a normal left renal collecting system and a right one that was capable of excreting miokon sodium but still hydronephrotic. She was well without pyelonephritis until she died of mesenteric arterial thrombosis 6 months after the exenteration of the pelvic organs.

CASE 3. B. H., a 53 year old woman, had received irradiation therapy for a squamous cell carcinoma of the cervix 8 years before she began to have vaginal bleeding, weakness, intermittent fever, melena, loss of weight, and oliguria.

When examined she had a blood pressure of 124/80 millimeters mercury and a pulse rate of 120 per minute. A mass filled the upper two-thirds of the vagina and protruded into the rectum. It was fixed to both pelvic walls. Intravenous pyelograms showed no miokon sodium in the left renal collecting system and little in the hydronephrotic right one. Serum nonprotein nitrogen concentration was 72 milligrams per cent; roentgenograms of the chest showed no metastases. A biopsy of the cervix was interpreted as fibrosarcoma of the uterus. An ileal-segment ureteral diversion and sigmoid colostomy were performed after operative exploration of the abdomen showed that no tumor existed outside the pelvis. Nonprotein nitrogen concentration was 30 milligrams per cent 10 days later. Exenteration of the pelvic organs was performed 19 days after ureteroileal urinary diversion. Only slight bilateral hydronephrosis remained 3 weeks after pelvic exenteration. Death ensued suddenly 6 months later of what was thought to be a cerebral hemorrhage. No autopsy was performed.

CASE 4. B. Y., a 32 year old woman, ill of persistent postirradiation carcinoma of the cervix, became completely anuric 3 days after a pyelographic examina-

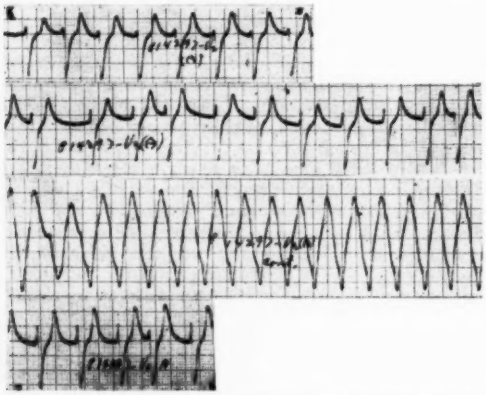


FIG. 2. Case 1. Electrocardiographic tracings of precordial leads V_2, V_3, and V_4 show ventricular tachycardia.

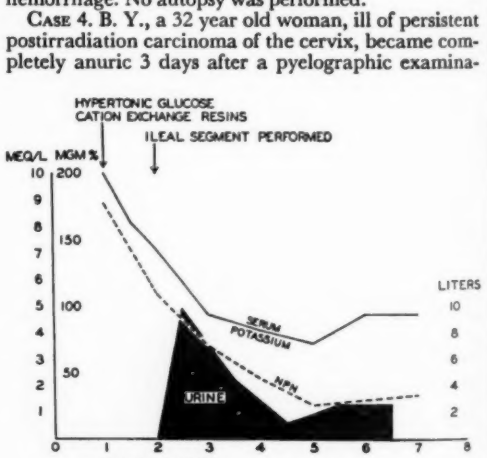


FIG. 3. Case 1. Graph illustrates the drop in serum concentrations of potassium and nonprotein nitrogen associated with the return of urine excretion after treatment with 20 per cent glucose in water intravenously, colonic irrigations containing a cation exchange resin, and ileal-segment urinary diversion.

a

FIG. 4.

b

FIG. 5.

FIG. 4. Case 4. Representative intravenous pyelograms show: a, Marked bilateral hydronephrosis 3 days before complete anuria developed. b, Hydronephrosis persistent 2 weeks after ureteroileal urinary diversion.

FIG. 5. Case 4. Intravenous pyelogram made 5 weeks after urinary diversion shows a normal right kidney and a left kidney which has poor concentrating capacity but is no longer hydronephrotic.

tion had shown no excretion of miokon sodium by the left kidney and a grade III right hydronephrosis (Fig. 4a). Because she had a serum nonprotein nitrogen concentration of 96 milligrams per cent and signs of uremia, a ureteroileal urinary diversion was performed after persistence of the carcinoma was proved and found to be limited to the pelvis. Renal excretory capacity improved postoperatively (Fig. 4b). Three weeks later a pelvic exenteration was performed and further improvement in renal status followed (Fig. 5).

One month after pelvic exenteration, the right kidney was normal, but the left kidney contained a palpable mass. The left kidney was removed and found to contain metastatic carcinoma. Right renal hypertrophy occurred following the left nephrectomy, indicating that the ureteroileal diversion functioned exceedingly well (Fig. 6). She died of metastatic carcinoma of the liver and many other organs 13 months after exenteration.

CASE 5. R. S., a 36 year old woman, had a postirradiationally persistent squamous carcinoma of the cervix with ureteral obstructive uremia. The cervix was a large ulcerated mass extending into the uterosacral ligaments and was completely fixed within the pelvis. Because she was comatose, bilateral nephrostomies were performed. Nonprotein nitrogen concentration promptly dropped from 165 to 18 milligrams per cent. Three weeks later the tumor was found to be removable by pelvic exenteration. A bilateral ureteroileal urinary diversion also was performed. Postoperatively, the nephrostomy sinuses closed quickly. Death resulted from osseous and pulmonary metastases 16 months after pelvic exenteration; there had been no difficulty attributable to the ureteroileal diversion.

CASE 6. G. B., a 35 year old woman, had a persistent squamous carcinoma of the uterine cervix (League of Nations II) after having been given two applications of radium (total 7,400 mgm. hours) to the cervix, a month apart, and an injection of radioactive colloidal gold into the parametrial tissues (130 millicuries).

A grade III left and a slight right hydronephrosis was discovered before irradiation therapy was begun. A month after completion of irradiation, the right kidney was normal but the left kidney remained hydronephrotic. Two weeks later she began to have urinary frequency, suprapubic pain, and dysuria and within 6 weeks had become oliguric. The carcinoma was found to have invaded the bladder and there was severe irradiation cystitis. During the subsequent 10 days she had intermittent, gross hematuria and the oliguria persisted. Nonprotein nitrogen concentration

FIG. 6. Case 4. Intravenous pyelograms: a, Before and b, 7 months after left nephrectomy. The right renal shadow in "b" is larger than it is in "a."

a b c d

FIG. 7

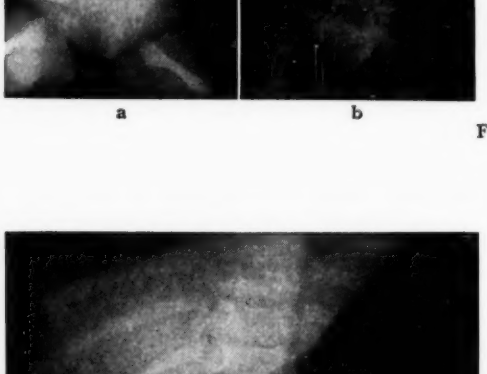
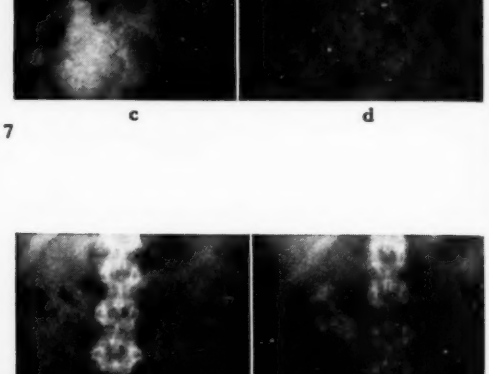


FIG. 8.



a b c d

FIG. 9.

FIG. 7. Case 7. Pyelographic roentgenograms show: a, A large hydronephrotic right kidney soon after birth (miokon sodium injected percutaneously). b, Persistent hydronephrosis 1 month after bilateral pyeloureteroplasty. c, Persistent hydronephrosis 1 month after bilateral ureteroneocystomy (the right nephrostomy still drained infected urine). d, Residual hydronephrosis 3 weeks after pelvi-ileal urinary diversion (the right nephrostomy had closed).

FIG. 8. Case 7. Intravenous pyelogram showing the renal status 11 months after urinary diversion. The improvement in renal status incident to urinary diversion has been maintained.

FIG. 9. Case 8. Representative intravenous pyelograms show: a, No excretion of miokon sodium by either kidney in a preoperative roentgenogram made 120 minutes after the injection of miokon sodium intravenously. b, Prompt excretion of miokon sodium by a hydronephrotic right kidney but none by the left kidney, 8 days after uretero-ileal urinary diversion. c, Residual hydronephrosis and excretory capacity 5 minutes and d, 35 minutes after the injection of miokon sodium intravenously 4 weeks after urinary diversion.

rose to 102 milligrams per cent and she began to vomit. Ileal-segment urinary diversion was performed after celiotomy showed the tumor to be confined to the pelvis. Two weeks later the renal collecting systems were nearly normal and nonprotein nitrogen concentration was 21 milligrams per cent. Three weeks after urinary diversion, the tumor was removed by exenteration of the pelvic organs. She was well for the next 4 months, but then a palpable tumor appeared in the right groin and she died of abdominal carcinomatosis 5½ months after pelvic exenteration.

CASE 7. D. L., a female negro infant, was born with very large congenital hydronephrosis of both kidneys. A nephrostomy was performed upon the right kidney when she was 3 days old, and bilateral pyeloureteroplasties were done 3 weeks later. However, a Pseudomonas aeruginosa pyelonephritis persisted and because of this a bilateral ureteroneocystostomy was performed at age 7 months. This failed to relieve the infection and she had chills and fever repeatedly. A bilateral ileal-segment urinary diversion was established 2 months after the ureteroneocystostomy. This was effected by anastomosing the left and right renal pelves to an isolated loop of ileum. The nephrostomy closed quickly, the bilateral hydronephrosis regressed rapidly (Figs. 7 and 8), and all signs of pyelonephritis disappeared. She is well at 2 years of age.

CASE 8. H. A., a 35 year old woman, had a persistence of carcinoma of the cervix after irradiation therapy. She had a large ulcerated mass replacing the cervix extending to both pelvic walls and narrowing the upper rectum. No pulmonary, nodal, or hepatic metastases were found. Intravenous pyelography was unsuccessful because of failure of the kidneys to excrete miokon sodium (Fig. 9). Nonprotein nitrogen concentration rose from 32 to 86 milligrams per cent during the first 3 days of hospitalization; drowsiness and generalized tissue edema developed, but significant oliguria was not recorded. A sigmoid colostomy and an ileal-segment urinary diversion were performed after the tumor was found to exist only in the pelvis. Postoperative diuresis (4,275 c.c. of urine in 24 hours) was followed by the disappearance of tissue edema, drowsiness, and uremia. The tumor was removed by pelvic exenteration 11 days after urinary diversion. Three weeks later, the right kidney was nearly normal but the left one was hydronephrotic and excreted miokon sodium poorly. She died of carcinomatosis 4 months after removal of the pelvic tumor.

SUMMARY OF CASES

Six emergency ureteroileostomies were performed upon anuric or oliguric, uremic persons having neoplastic obstructions of the pelvic ureters. Two other ureteroileal urinary diversions were established after nephrostomy; one for neoplastic occlusion of the pelvic ureters, the other for irreparable congenital ureteropelvic obstructions with bilateral hydronephrosis. In the last case, the renal pelves were anastomosed to an isolated segment of ileum. The ureteroileal diversions were immediately functional in all cases and remained so until the death of 7 of the 8 patients. The child with the bilateral ureteropelvic obstruction is still well 15 months postoperatively. No deaths were attributable to the urinary diversion.

DISCUSSION AND CONCLUSIONS

Emergency bilateral ureteroileal urinary diversion is an effective and safe means of treating the uremia associated with irreparable bilateral ureteral obstruction. It permits recovery from uremia and thereby affords the surgeon or radiologist an opportunity to treat neoplasms that have completely obstructed the pelvic ureters. The preliminary ureteroileal diversion relieves the renal decompensation and subsequently allows extensive pelvic operations to be performed safely.

Whenever the continuity and the function of the lower urinary tract cannot be re-established, diversion of the ureters into ileal segments is preferable to nephrostomy excepting if severe uremia exists. If uremia is severe, unilateral nephrostomy is preferable to ureteroileal urinary diversion because nephrostomy is more quickly performed, is not attended by as much postoperative ileus as is ureteroileal diversion, and the danger of breakdown of anastomoses does not exist. Of course, ureteroileal diversion of urine should not be employed whenever reconstitution of the lower urinary tract may be possible.

Ureteroileal diversion allows the surgeon to determine the cause of ureteral obstruction, the feasibility of its correction, and the extent of the neoplasm if one exists.

Reviews of New Books

THE MONOGRAPH *Tumours of the Bladder*[1] is the second volume in a series entitled *Neoplastic Disease at Various Sites*. This volume is ably edited by D. M. Wallace. The book is divided into 21 chapters which are in turn grouped into 7 sections. Fourteen authors have contributed to the text, and this has permitted an exhaustive coverage of the subject. In this volume, the public health aspects of tumors of the urinary bladder, including their occurrence as an industrial hazard, are discussed in detail. The present state of knowledge with regard to the induction of bladder tumors by various aromatic amines, as well as the possible significance of the metabolic products of tryptophan metabolism in this regard is clearly and concisely presented.

The major portion of the book deals with a detailed presentation of the current impressions and practices of authors with considerable experience in the care of patients with bladder tumors. For example, in the section dealing with the pathology of bladder tumors, the initial chapter presents and discusses the scheme utilized in classifying bladder tumors at the Institute of Urology of the University of London. In a subsequent chapter, a discussion of subjects of practical importance such as methods employed in fixing surgical specimens for study is presented. A detailed, well illustrated description of the gross and histologic features utilized in classifying bladder tumors is given.

These chapters are followed by others in which the behavioral pattern of bladder tumors and the findings in 150 postmortem examinations on patients with carcinoma of the urinary bladder are discussed. It is interesting to note in the latter study that two-thirds of the tumors infiltrating bladder muscle superficially showed no evidence of spread; none of the deeply infiltrating tumors were without evidence of spread. Analysis of the modes of death in patients with carcinoma of the bladder, presented in the next chapter, revealed that renal damage was the major factor.

The section devoted to pathology is followed by one in which the Editor of this monograph presents a very practical discussion of the desirable preoperative evaluation of patients with neoplasms of the urinary bladder. The techniques of biopsy and bimanual examination are described; the method of staging employed by the author is presented in detail.

The final two sections of the book are devoted to methods of surgical treatment and an analysis of treatment. The indications for and techniques of endoscopic therapy, partial cystectomy, total cystectomy, and radical cystectomy are discussed. Of interest is the continued preference of the Editor for ureterocolic anastomosis over other forms of urinary diversion. One of the chapters in the section on treatment is devoted to radiotherapy. This is apparently a popular form of treatment for bladder tumors in Great Britain; radiotherapy was used as the first part of planned treatment in nearly every case from one of the hospitals contributing clinical material for analysis for this publication. The indications for and techniques of intracavitary irradiation, interstitial implantation, and external beam therapy are presented in an understandable fashion. In the section analyzing treatment the data from 1,420 new cases of bladder tumor seen from 1950 to 1956 are presented; the relationship of sex, age, history, tumor type, and survival is the subject for one chapter. The results of treatment are presented in a unique fashion. A simple graph is utilized for demonstrating crude survival rates; a line chart is utilized to give survival information and often tumor stage in each patient subjected to a particular treatment. These charts require more than a casual perusal but do succeed in presenting a good deal of information clearly in a concise manner. As the authors point out, the differences in the results of the various types of treatment in a series such as this in which patients are selected for each type of therapy can have little significance with regard to judging the value of the therapy employed. As one surveys these results, the predominant influence of tumor stage in determining the patient's survival once again seems apparent.

This monograph summarizes clearly most that is known about tumors of the urinary bladder. As in any volume with contributions from several authors, there is some duplication of material and occasionally some lack of continuity. In general, the material is presented clearly and is well illustrated. Both the theoretic and practical aspects of bladder tumors are considered in detail. This combined approach makes this a unique book which should appeal to those with a special interest in genitourinary or neoplastic diseases.

—John T. Grayhack.

[1]NEOPLASTIC DISEASE AT VARIOUS SITES. Edited by D. W. Smithers, M.D., F.R.C.P., F.F.R. TUMOURS OF THE BLADDER, Edited by David M. Wallace, O.B.E., M.S., F.R.C.S. Vol. II. 352 pages, 202 illustrations. $11.50. Edinburgh and London: E. & S. Livingstone Ltd.; Baltimore: The Williams & Wilkins Co., 1958.

THE EXHAUSTIVE LITTLE BOOK *Surgery of Cancer of the Colon and the Rectum*[2] is replete with vivid illustrations of the many problems arising in the diagnosis and treatment of cancer of the colon and rectum. Its subject matter is divided into three parts, the first of which reviews the general picture of colon and rectal cancer, and is followed by a complete study of the anatomy, physiology, and anatomicopathologic considerations pertinent to the specific surgical approach involved. The last, and by far the greater part of the book concerns surgical techniques used in handling varied issues seen in colon and rectal disorders.

The techniques are given in detail and illustrated with apt drawings. The various locations in which the tumor may be found are discussed, and the surgical method of eradicating the growth is given particular emphasis. The section on colectomy is excellently done and gives credit to the wide experience of the authors. This portion of the book and the following chapters may be used as an operative atlas, the narrative detail generously complementing the accurate illustrations. The historical background of the various procedures is interesting and throws considerable light on the development of the techniques as currently practiced. Many appreciative comments are interspersed throughout the material giving an authoritative critique of the subject under discussion.

The style is fluent and very readable. Any surgeon would consider this work a worthwhile addition to his library. —*Stephen A. Zieman.*

THE FOURTH EDITION of *Lehrbuch der Geburtshilfe*[3] which appears 3 years after the previous one has 24 fewer pages and 9 fewer illustrations. The new collaborator is H. Hartl rather than W. Bickenbach, but the faithful and excellent artist Käthe Droysen, remains. In this edition, the author still retains descriptions and illustrations of old-fashioned instruments for taking internal pelvic measurements and for compression of the aorta to control uterine hemorrhage.

The chief effort in this edition was to correlate the data in such a way as to be acceptable to both practicing physicians and young medical students. The section on the toxemias of pregnancy was completely rewritten. The syndrome of afibrinogenemia is now fully described. New data have also been added about the physiology and pathology of the newborn, the adverse effects of diabetes on the infant, the bad effects of hypoxia on the child, and the differential diagnosis of icterus of the newborn. The chapters on "Embryology" and "Physiology and Pathology of the Newborn" were prepared by G. Martius.

There is no doubt that this book will continue its well deserved popularity because the senior author and his collaborators have had extensive experience in both practical obstetrics and in the teaching of this subject. —*J. P. Greenhill.*

[2]CIRUGIA DEL CANCER DEL COLON Y DEL RECTO. By Dr. J. Pi-Figueras. With the collaboration of Drs. V. Artigas, P. Anfres, and A. Gimenez-Salinas. 562 pages, 314 illustrations. Barcelona, Madrid, Buenos Aires, Mexico, Caracas, Bogotá, and Rio De Janeiro: Salvat Editores, S.A., 1958.

[3]LEHRBUCH DER GEBURTSHILFE. By Prof. Dr. Heinrich Martius. Assisted by Prof. Dr. H. Hartl and Käthe Droysen. 4th ed. 731 pages, 768 illustrations. $14.20. Stuttgart: Georg Thieme Verlag, 1959.

TWENTY-EIGHT AUTHORITIES with wide experience in the treatment of cancer have contributed to the excellent book entitled *Cancer; Diagnosis and Treatment.*[4] The text is composed of 20 chapters, each consisting of approximately 30 pages. The print is large, easily readable, and for the most part does not exceed 39 lines to the page. The illustrations, charts, and tables are excellent.

Both the common and uncommon forms of cancer are thoroughly presented. An attempt has been made to avoid partisanship in regard to the controversy of surgery versus radiation therapy. The chapters are compact and meaty, and lengthy discussion of theory has been sacrificed to practicality.

The first 2 chapters are of a more or less general and introductory nature and deal with the current status of management of the cancer patient and the medical and psychologic management of his manyfold problems. The importance of frankness and the avoidance of scientific austerity on the part of the physician are basic principles in dealing with cancer patients.

Chapter 3 deals with the large field of tumors of the head and neck, including the face and scalp, the mouth, lip, palate, accessory sinuses, pharynx, larynx, salivary glands, thyroid and parathyroid glands, and jaws. It is in this group that particularly gratifying results may be obtained by the intelligent co-operation of surgeon and radiologist.

Chapter 4 on tumors of the breast stresses the advantages of a small wedge biopsy over excision of a tumor for biopsy, and deplores the use of aspiration biopsy. The common and uncommon breast tumors encountered are well described. The location of the tumor, the course of metastases, and their relation to the type of treatment indicated are well presented.

Chapter 5 on tumors of the chest is concerned primarily with lung tumors, their diagnosis and treatment. The reviewer would credit greater value to scalene node biopsy in the absence of palpable nodes, but the chapter is well written and authoritative. Included also is a short discussion of mediastinal and esophageal tumors.

Chapter 6 on tumors of the stomach is an excellent review of the subject. Of particular interest are the authors' proposals for improvement of therapeutic results by instituting treatment at a time when the lesion is not yet diagnosable by present day means.

Chapter 7 is a fairly standard review of tumors of the small intestine, liver, gallbladder, bile ducts, and pancreas.

Chapter 8 on tumors of the colon, rectum, and anus is very well done. The dangers and foolhardiness of attempts to avoid colostomy in the treatment of rectal cancer are again stressed.

Chapter 9 concerns the diagnosis and management of tumors of the kidney, ureter, bladder, and adrenals; and chapters 10 and 11 are devoted to tumors of the female and male generative tracts.

Chapter 12 on bone tumors should prove of especial value to physicians other than orthopedic surgeons in the differentiation by exclusion of the various bone diseases.

[4]CANCER; DIAGNOSIS AND TREATMENT. Edited by John B. Field, M.D., Ph.D. With 28 contributors. 796 pages, illustrated. $18.50. Boston: Little, Brown & Co., 1959.

Chapter 13 is an excellent but brief review of tumors of the brain and spinal cord, their diagnosis, differential diagnosis, and treatment by surgery and radiation therapy.

Chapter 14 on tumors of the skin contains a unique table of benign tumors arranged as a diagnostic key depending on criteria of site of origin, age of appearance, and frequency of occurrence, including recommended management.

Chapter 15 is little more than a brief outline of tumors of the soft parts, but chapter 16 covers adequately the diagnosis and treatment of tumors of the lymphatic system including assorted lymphomas.

Chapter 17 on neoplastic diseases of the blood and bone marrow is devoted mostly, as one might expect, to leukemia.

Chapter 18 presents a general review of cancer in children and the two final chapters are devoted to the present status of chemotherapy of cancer and radiotherapy of cancer.

Throughout the book one is impressed with the fact that cancer is not a single entity but rather a multiplicity of diseases. To treat cancer properly one must understand the life history of each type of cancer. The proper treatment of each case must be selected and carried out with regular follow-up examinations.

Any physician will find this book a valuable and often referred to guide in the management of cancer patients. The reviewer knows of no other single volume in which so much information on cancer is condensed and readily available in such a small space.

—Edward W. Gibbs.

A COMPREHENSIVE REVIEW of one of the most advanced and informative techniques performed for the evaluation of pulmonary function is presented in the volume entitled *The Investigation of the Relative Function of the Right and Left Lung by Broncho-Spirometry.*[5]

This 145 page monograph summarizes the experiences gained in the performance of 300 bronchospirometric procedures. The subject is presented simply and there are adequate diagrams, drawings, and reproductions of spirometric tracings to make easy reading for those interested in pulmonary physiology, but not actually performing bronchospirometry.

The author first describes the equipment used, including the new plastic tube devised by himself, and the technique of performing the examination as well as the technical errors to be avoided. He then demonstrates the physiologic alterations brought about by increased work loads and changes in position of the patient from supine to lateral and upright. Finally, he presents data associated with pulmonary tuberculosis and carcinoma with the results of preoperative and postoperative bronchospirometric findings with the associated findings of cardiac catheterization and angiocardiography.

The material is broken down into brief 3 or 4 page chapters. This simple style of presentation, along with the ample illustrations, makes this book pleasant reading and a valuable addition to the bookshelf of one who daily depends on bronchospirometric finds in the preoperative evaluation of his patients.

In addition to occasional chapter summaries, a final review of the data and conclusions is given. A full bibliography is appended.

—Frank J. Milloy.

IT WAS MY PRIVILEGE to review the first edition of *Surgical Pathology.* All the complimentary remarks made at that time may be repeated with reference to the second edition.[6]

First, without in any way interfering noticeably with weight, binding, or printing, there are 260 additional pages. This allows for more photographs, photomicrographs, charts, tables, and discussion.

Harvey R. Butcher, Jr., of the Department of Surgery, Washington University, St. Louis, has collaborated extensively with the author. Scattered diffusely through the entire volume is evidence of this under the heading "Clinico-pathologic Correlation." Butcher has also written a complete chapter on "Wound Healing."

David E. Smith, now at the University of Virginia, has revised his chapter on the central nervous system; L. E. Zimmerman of the Armed Forces Institute of Pathology has written a new chapter on the "Surgical Pathology of the Eyes and Ocular Adnexa"; Robert Ogilvie, of St. Louis' St. Luke's Hospital, has reorganized the section on non-neoplastic conditions of the skin originally written by the late Zola K. Cooper.

Surprisingly enough, all of these sections blend well and there is no tendency to disagreement.

As might be expected, there is some undue emphasis upon tumors, but this may only indicate the authors' interests. Certainly, tumors constitute a large part of the surgeon's practice. Even so, there is no hesitancy in recommending the use of radiation in treatment of some conditions.

There is a definite practical approach. In most areas the use of frozen sections and their diagnostic accuracy are explained. Cytologic investigations are also delineated. The methods to open and to handle some more important specimens are included. Fixatives and stains are mentioned briefly.

Some roentgenograms and clinical photographs are used where indicated. Both macrophotographs and photomicrographs are well reproduced and contribute to the identification of lesions.

All regions are capably discussed. I especially liked the ones on head and neck, chest, gastrointestinal tract, bone, connective tissue, eye, and malignant tumors of the skin. There is a splendid résumé of the subject of carcinoma arising in gastric ulcer which justifies perusal by any physician or any medical student.

The residents, the clerks, and the sophomore students have used the first edition constantly. Undoubtedly, the second edition will be as readily accepted.

This is a very comprehensive volume which may be recommended without hesitancy.

—Mark C. Wheelock.

[5]THE INVESTIGATION OF THE RELATIVE FUNCTION OF THE RIGHT AND LEFT LUNG BY BRONCHO-SPIROMETRY; TECHNIQUE, PHYSIOLOGY, AND APPLICATION. By Frank Bergan, M.D. 145 pages, 85 illustrations. $4.50. New York and London: Grune & Stratton, Inc., 1958.

[6]SURGICAL PATHOLOGY. By Lauren V. Ackerman, M.D. In collaboration with Harvey R. Butcher, Jr., M.D. 2nd ed. 1096 pages, 1114 illustrations. $15.00. St. Louis: The C. V. Mosby Co., 1959.

THE BOOK by Pack and Ariel entitled *Tumors of the Head and Neck*,[7] is a complete and authoritative treatise on the treatment of all tumors in this area, exclusive of brain tumors. As noted in the preface, "In no field of oncology is a greater demand placed upon the physician than in treating cancer of the head and neck. Because of its protean problems, no one method of management can be declared the best. In this book, the Editors have presented all therapeutic methods, whether radical or conservative, at present acceptable for tumors of the head and neck. . . . Authors have been drawn from treatment centers over the world; South Africa, Canada, England, Sweden, Denmark, and France are represented as well as the United States."

Various types of surgical treatment and alternative methods of radiologic treatment, as well as combinations of these two modalities, are described in detail for many lesions. In addition to this, attention is given to the importance of functional results and methods of plastic surgical repair. As noted on page 93, "It is the promise of acceptable cosmetic and functional repair that prompts the patient to submit to deforming procedures about the face."

The 70 authors of this book are well known leaders in the field of cancer surgery of head and neck. As in any compilation of this sort, there are some instances of disjointedness, some gaps, some contradictions, but also the very great advantage of differing points of view. The book is so important that it belongs in the library of every physician who is engaged in, or studying, this particular field of surgery.

—*Frank McDowell.*

THE STANDARDS of the preceding two volumes of this set on *Cancer* are maintained in the third volume.[8] In outline, it continues with some extension from Volume II which was devoted to pathology. There are 4 chapters, one on "Immunological Aspects", one on "Cancer Cells in Tissue Culture", one on "Malignant Disease of Domesticated Animals", and one on "Statistical Investigations Concerning Causation of Various Forms of Human Cancer." All are excellent, clearly presented, and done by authors especially interested in the respective topics. The one on the cancer in domesticated animals is interesting and informative.

One section is assigned to Geography of Cancer. The introduction done by Paul Steiner, who is known for his studies on this subject, is splendid. The others deal with various regions in the world—England and Wales, United States of America, Africa, Denmark, Iceland, and India. Emphasis is placed on habits of eating, smoking, and chewing; and on customs concerning early or late marriage; nursing; circumcision; and bathing, or cleanliness. Although distinct conclusions are not drawn, still there are inferences that all of these are factors in the development of forms of cancer.

There are four chapters on Occupational Cancer—one each on "Leukemia", "Skin", and "Urinary Bladder" and one on the "Medico-Legal Aspects." These should be "must reading" for industrial physicians and for compensation boards.

There is also a section on Cancer Education. Comparisons are drawn between various medical schools and in postgraduate training, especially in the United States. There is no true deficiency for those who wish special instruction. However, a suggestion is made that a combination of horizontal and vertical teaching in the various medical schools would result in students knowing more about cancer in general and appreciating its importance. There are also chapters on the "Public Education in Great Britain and in the United States."

A final part of this volume deals with detection. Cancer centers, simple cancer examinations, and cytodiagnosis are all discussed. Stress is laid on the attempt to determine the presence of a cancer in the more commonly involved organs.

—*M. C. Wheelock.*

WITHIN THE PAGES OF THE COMPACT BOOK entitled *Office Gynecology*[9] is found a wealth of practical information on techniques of diagnostic and therapeutic office gynecology. Though brief, it covers nearly all aspects of its title. The entire book has been revised since the previous edition appeared 5 years ago and emphasis is placed on prophylaxis and early diagnosis of diseases of the pelvis. New chapters have been added on office pediatric and geriatric gynecology and on intersexuality.

Chapters on endocrinology and artificial insemination would be especially useful to physicians who occasionally treat patients with such problems. Two chapters which are especially recommended are those on psychosomatic gynecology and premarital examination and advice.

Greenhill's deep understanding and lucid style of writing as well as his wide experience in gynecology make this a useful book to general practitioners and gynecologists alike. It is well illustrated.

—*Charlotte Herman Kerr.*

THE FIRST EDITION of Kneise and Schober's *Roentgenological Examination of the Urinary Organs* appeared in 1941. Professor Kneise died in 1953 before the appearance of the fourth edition. The present, fifth,[10] edition has been revised and brought up to date by the former junior author, Dozent K. L. Schober, with the assistance of Privatdozent U. Schneider, of the Department of Roentgenology of the University of Munich. The methods of examination and x-ray procedures are briefly but clearly presented, including the newer techniques such as aortography, tomography, and retroperitoneal gas insufflation.

[7] TREATMENT OF CANCER AND ALLIED DISEASES. TUMORS OF THE HEAD AND NECK. Edited by George T. Pack, M.D., F.A.C.S., and Irving M. Ariel, M.D., F.A.C.S. 2nd ed. Vol. III. 781 pages, illustrated. $30.00. New York: Paul B. Hoeber, Inc., Med. Book Dept. of Harper & Bros., 1959.

[8] CANCER. Edited by Ronald W. Raven, O.B.E.(Mil.), T.D., F.R.C.S. Vol. III. Part III—Additional Pathological Aspects, Part IV—Geography, Part V—Occupational Cancer, Part VI—Cancer Education, Part VII—Cancer Detection. 501 pages, 165 illustrations. $18.00. London: Butterworth & Co., Ltd., 1958.

[9] OFFICE GYNECOLOGY. By J. P. Greenhill, B.S., M.D., F.A.C.S., F.I.C.S. (Hon.). 7th rev. enl. ed. 572 pages, 145 illustrations. $9.00. Chicago: The Year Book Publishers, Inc., 1959.

[10] DIE ROENTGENUNTERSUCHUNG DER HARNORGANE. By Dr. Med. O. Kneise and Dr. Med. K. L. Schober. With the assistance of Dr. Med. U. Schneider. 5th rev. ed. 328 pages, illustrated. geb. D.M. 55 Leipzig: Veb Georg Thieme, 1958.

The 401 illustrations include a few drawings in color as well as a great variety of roentgenograms which are superbly reproduced. Each illustration is accompanied by a brief case history, and a short description of the salient characteristics of the abnormalities which identify the particular pathologic condition present.

This volume is well written and very easy to read. It should be of interest to the urologic resident and the practicing urologist. —*Frederick A. Lloyd.*

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

TRAUMA. By Harrison L. McLaughlin, M.D. 784 pages, illustrated. $18.00. Philadelphia and London: W. B. Saunders Co., 1959.

DISEASES OF THE NOSE, THROAT, AND EAR. Edited by Chevalier Jackson, M.D., Sc.D., LL.D., L.H.D., F.A.C.S. With the collaboration of 61 authorities. 2nd ed. 886 pages, 1,193 illustrations. $20.00. Philadelphia and London: W. B. Saunders Co., 1959.

LEHRBUCH DER KRANKENGYMNASTIK. Edited by Prof. Dr. K. Lindemann, Dr. H. Teirich-Leube, and Dr. W. Heipertz, Vol. I. Einfuehrung in die Krankengymnastik Physiologie; Krankheitslehre Grundlagen und Grundtechnik der Krankengymnastik und Massage. 328 pages, illustrated. $6.50. Stuttgart: Georg Thieme Verlag, 1959.

ADÉNOMECTOMIE ENDO-URÉTRALE DE L'ADENOME PROSTATIQUE ET TRAITEMENT DU CANCER DE LA PROSTATE. By Raymond Denis. 194 pages, 100 illustrations. 2,500 fr. Paris: Masson & Cie, 1959.

THE GREAT PULSE; JAPANESE MIDWIFERY AND OBSTETRICS THROUGH THE AGES. By Mary W. Standlee. 192 pages, illustrated. $4.50. Rutland, Vermont, and Tokyo, Japan: Charles E. Tuttle Co., 1959.

IL MIOFIBROMA DELL'UTERO DAL PUNTO DI VISTA PATOGENETICO. By Prof. Espedito Moracci. 223 pages, 31 illustrations. L. 2,500. Pavia, Italy: Aldo Garzanti Editore, 1958.

PSYCHOSOMATIC METHODS IN PAINLESS CHILDBIRTH; HISTORY, THEORY AND PRACTICE. By L. Chertok. Translated from the 2nd French edition by Denis Leigh, M.D. 260 pages. $6.50. New York, London, Paris, Los Angeles: Pergamon Press Inc., 1959.

PROGRESS IN HEMATOLOGY. Edited by Leandro M. Tocantins, M.D. Vol. II. 290 pages, illustrated. $9.75. New York and London: Grune & Stratton, Inc., 1959.

METALS AND ENGINEERING IN BONE AND JOINT SURGERY. By Charles Orville Bechtol, M.D., Albert Barnett Ferguson, Jr., M.D., and Patrick Gowans Laing, M.B., B.S., F.R.C.S. 186 pages, 119 illustrations. $8.00. Baltimore: The Williams & Wilkins Co., 1959.

SURGERY OF THE FOOT. By Henri L. DuVries, M.D. 494 pages, 403 illustrations. $12.50. St. Louis: The C. V. Mosby Co., 1959.

A MANUAL OF BANDAGING, STRAPPING AND SPLINTING. By Augustus Thorndike, M.D., F.A.C.S. 3rd ed. 153 pages, 125 illustrations. $2.75. Philadelphia: Lea & Febiger, 1959.

TRANSPLANTATION OF TISSUES; SKIN, CORNEA, FAT, NERVES, TEETH, BLOOD VESSELS, ENDOCRINE GLANDS, ORGANS, PERITONEUM, CANCER CELLS. Edited by Lyndon A. Peer, M.D. Vol. II. 690 pages, 252 illustrations. $20.00. Baltimore: The Williams & Wilkins Co., 1959.

TEXTBOOK OF ORAL SURGERY. Edited by Gustav O. Kruger, D.D.S., F.A.C.D. 573 pages, 489 illustrations. $12.75. St. Louis: The C. V. Mosby Co., 1959.

NEUROLOGICAL COMPLICATIONS OF LYMPHOMAS AND LEUKEMIAS. By Henry M. Williams, M.D., Henry D. Diamond, M.D., F.A.C.P., Lloyd F. Craver, M.D., F.A.C.P., and Herbert Parsons, M.D. 134 pages, illustrated. $5.75. Springfield, Ill.: Charles C Thomas, 1959.

HERNIA. By Sir Heneage Ogilvie, K.B.E., M.D., F.R.C.S. 135 pages, 51 illustrations. $6.50. London: Edward Arnold (Publishers) Ltd., 1959; Baltimore: The Williams & Wilkins Co., exclusive U. S. agents.

NOTES OF A SOVIET DOCTOR. By G. S. Pondoev. 238 pages. $4.95. New York: Consultants Bureau, Inc.; London: Chapman & Hall, Ltd., 1959.

MIND IF I SMOKE? By Harold Shryock, M.A., M.D. 138 pages, illustrated. Mountain View, Calif.: Pacific Press Publishing Ass., 1959.

BASIC SURGERY. Edited by Leslie Oliver, M.B., F.R.C.S. (Eng.), F.A.C.S. 1359 pages, 680 illustrations. $26.50. Springfield, Ill.: Charles C Thomas, 1959.

CARE OF THE SURGICAL PATIENT. By Jacob A. Glassman, M.D., F.A.C.S., F.I.C.S., and Raymond W. McNealy, M.D., F.A.C.S., F.I.C.S. 320 pages, 3 illustrations. $6.50. Baltimore: The Williams & Wilkins Co., 1959.

MOLOY'S EVALUATION OF THE PELVIS IN OBSTETRICS. By Charles M. Steer, M.D., F.A.C.S., F.A.C.O.G. 2nd ed. 131 pages, 57 illustrations. $4.00. Philadelphia and London: W. B. Saunders Co., 1959.

RADIATION THERAPY. By Walter T. Murphy, M.D. 1041 pages, illustrated. $25.00. Philadelphia and London: W. B. Saunders Co., 1959.

CANCER IN FAMILIES; A STUDY OF THE RELATIVES OF 200 BREAST CANCER PROBANDS. By Douglas P. Murphy, M.D., and Helen Abbey, Sc.D. 76 pages. $2.50. Cambridge, Mass.: Published for The Commonwealth Fund by Harvard University Press, 1959.

LOW INTENSITY RADIUM THERAPY. By Charles L. Martin, E.E., M.D., F.A.C.R., and James A. Martin, M.D., F.A.C.R. 256 pages, 118 illustrations and 20 color plates. $12.50. Boston and Toronto: Little, Brown & Co., 1959.

TEXTBOOK OF PEDIATRICS. Edited by Waldo E. Nelson, M.D., D.Sc. 1462 pages, 427 illustrations. $16.50. Philadelphia and London: W. B. Saunders Co., 1959.

COLLECTED PAPERS OF THE MAYO CLINIC AND THE MAYO FOUNDATION. Compiled by George G. Stilwell, A.B., M.D. Vol. L—1958. 791 pages, illustrated. $13.00. Philadelphia and London: W. B. Saunders Co., 1959.

AN ATLAS OF NORMAL RADIOGRAPHIC ANATOMY. By Isadore Meschan, M.D. Assisted by R. M. F. Farrer-Meschan, M.B., M.D. 2nd ed. 759 pages, 1446 illustrations. $16.00. Philadelphia and London: W. B. Saunders Co., 1959.

COLE & ELMAN'S TEXTBOOK OF SURGERY. By Warren H. Cole, M.D. With 49 contributing authors and consultants. Foreword by Evarts A. Graham. 7th ed. 1224 pages, illustrated. $17.00. New York: Appleton-Century-Crofts, Inc., 1959.